Vol. 25 No. 122 June, 1950

ARCHIVES OF DISEASE IN CHILDHOOD

INCORPORATING THE BRITISH JOURNAL OF CHILDREN'S DISEASES

CONTENTS

LONDON
BRITISH MEDICAL ASSOCIATION
TAVISTOCK SQUARE, W.C.1

Yearly Subscription (4 Numbers) 30s. U.S.A. $5.00 Single Number 7s. 6d.

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FOETAL PHYSIOLOGY AND CHILD HEALTH*

BY

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(RECEIVED FOR PUBLICATION, JANUARY 11, 1950)

It is my duty and pleasure to offer to the British Paediatric Association my thanks for the honour conferred on me by their invitation to deliver this lecture, the more so as it is the occasion of a joint meeting with the Society of Medical Officers of Health, whose Child Welfare Group has done such notable work in translating into administrative medicine the findings of the clinician and the laboratory workers. I hope what I have to say will be worthy, not only of the occasion, but of the great clinician in whose name this lecture has been founded.

George Frederick Still, whose memory it is my privilege to honour to-day, was physician in charge of the Department of Paediatrics at King's College Hospital, and physician to the Hospital for Sick Children, Great Ormond Street. He was the outstanding paediatrician of his time. He was small of stature, quiet, without bombast, but nevertheless replete with personality; a great clinician whose powers of observation, examination, and deduction at the bedside enabled him to advance his subject in a manner given to few of us. He was not an experimental physician in the modern style, far from it, nevertheless he did not disdain the aid to be obtained from the clinical laboratories. His influence on the medicine of his time was outstanding, and we may well pay testimony to-day to the fact that he was a power for health in the child of his generation, and in the child and adult of this and future generations.

The Problem

My task this afternoon is to show some ways in which the study of the physiology of the foetus can guide us in the preservation of the best health in the child and in after life. While the tag *mens sana in corpore sano* is true and the roots of mental disorder may strike back to intra-uterine life and earlier, I will restrict myself to the pre-natal development of the *corpus sanum*.

Methods of Study

In this lecture I am frankly stating the point of view of the laboratory worker. I can only give pointers to the clinician on possible ways of solving his problem. It is important to remember always that the clinician and the specialist in the preservation of child health—whether he be paediatrician, medical officer of health, or social worker—provides the problem in the vast majority of cases, though the first class scientist can, as in all branches of science, see his own problem. The physician is a biologist providing the spark which ignites the physiologist. The physiologist is often a dissatisfied clinician seeking new methods of approach to the problems before him.

There are two lines of approach, observational and experimental, and both are applicable to man as well as to animals. In each type the essence is the application of the principle of scientific method. An experiment may, of course, be one provided by nature, whether by famine, war, or other cataclysm. Many such have occurred in Europe and Asia during the war; they become experiments when observed methodically and scientifically.

It is worth while here to point out that experiments on man are of two types: the therapeutic, where some procedure is initiated and designed to benefit the individual patient, a reasoned and hopeful step; and the investigational one, in which the objective is primarily for the benefit of mankind and not necessarily for the patient. Of the most finished of these are the investigations of McCance, in which comparisons are made of the body fluids of the adult and the newborn infant (McCance, 1946; Jones and McCance, 1949). In fact, in many cases one must resort to observations and experiments on animals. For animal experiments to yield results applicable to man and to avoid fallacies, three criteria must be satisfied. (1) There must be such similarity of species that there is structural, biochemical, and functional resemblance to man. (2) There must be similar reactions in animals and man to the same changes in environment and the same experimental

* The Still Memorial Lecture, November 21, 1949.

procedures. (3) It being still a question of probability and not certainty, there must be available the experience of the human application before results are finally accepted.

Techniques and Procedures

Apart from observations, there are two major types of experimental approach in animals and man in the field we are discussing. These are the use of the whole animal and of caesarean section under anaesthesia. The latter approach was first used by Cohnstein and Zuntz in 1884, and was revived in 1923 at St. Thomas's Hospital Medical School, London. It rapidly spread after the publication of the first results in 1927 (Huggett, 1927). In the hands of Eastman and Kellogg in the United States, and of Barcroft and Barron at Cambridge, it has spread over the whole field. By this procedure it has been possible to treat the unborn foetus as an entity and to study it at any foetal age at leisure. It has been of particular service in the study of the placental mechanisms, since retraction of the placenta does not occur. It is, however, particularly suitable for foetal investigations, since, by using large animals such as sheep, the foetus is of a convenient size unobtainable in most laboratory animals. The anaesthetized mother is delivered by section in a bath of saline at body temperature and the foetus kept submerged in the saline outside the abdomen and attached to the unretracted placenta by the pulsating umbilical cord: in other words, conditions are almost (with the substitution of saline for amniotic fluid) identical with those *in utero*.

Observations can be made not only with the eye, but also by any suitable recording apparatus, whatever method of experimental procedure is adopted. Quite understandably, accurate precision biophysical techniques are used more and more as they become available. Here it is fundamental to bear in mind that the mere use of expensive and highly accurate and modern apparatus does not in itself alone ensure accuracy of work. Three other things are required in a biologist using accurate physical apparatus, such as photo-electric recorders, electronic amplifying valves, and Geiger-Müller counters for radioactive isotopes. These are skill, experience, and the biological training to interpret and assess the results and controls at their true value. In this case the word ' biological ' does not mean clinical ; it means functional biology in the old-fashioned sense of the word, namely, the fusion of physiology, zoology, and botany. In addition to this, it cannot be over-emphasized that most important of all is the sound biological training needed to plan and design the right experiment to give results and answers of value.

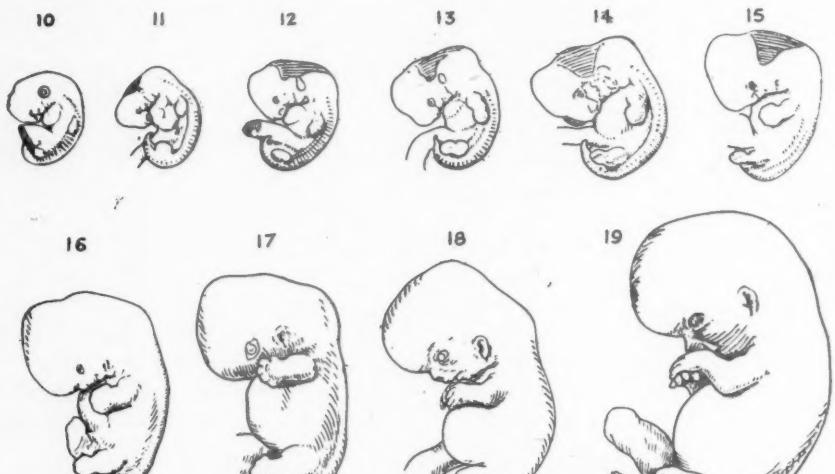


FIG. 1.—The size, shape, and proportions of the human foetus from the 7 mm. stage to full term, showing different parts growing at different rates in succeeding stages, the head preceding the trunk, the fore limbs rather faster than the hind limbs (Fig. 225, *Kollmann's Handatlas des Entwicklungsgeschichte*, 1907).

Basic Material

Theory of Pattern and Gradient in Development. D'Arcy Thompson (1916) in his classic ' Growth and Form ' shows that growth is an orderly and progressive change, subject to definite laws, but varying in rate and degree along definite ' gradients ' of growth. The variation in rate in different directions determined the ' form ' of the organism. C. M. Child (1941), the American zoologist, showed that these gradients, whether spreading outwards or arranged along an axis with poles (polarity) at each end, were present not only in the organism as a whole, but in portions and even in cells. Further, the gradient was shown by all functional components: oxygen consumption, metabolic rate, enzyme activity, and protein deposition, to mention a few. These gradients are controlled by intrinsic factors, genetic and species, and by extrinsic factors,

diet and environment. We see this theory exemplified when we look at growth from conception to adulthood and the rates of growth of different embryonic organs.

Theory of Partition of Nutrients. Hammond (1944) has put forward this theory based on the work of Thompson and Child. It is unproven, but it is a good working hypothesis based on the facts as known, and has withstood the criticism of Barcroft (1946).

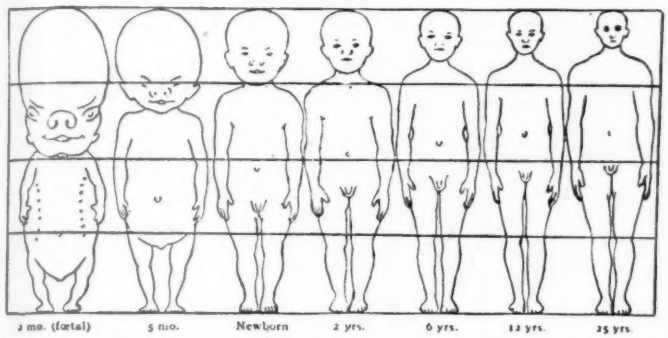


FIG. 2.—The changing proportion of the human body during prenatal and postnatal growth (Fig. 112, 'Developmental Anatomy,' Arey, 1934).

The foetus and placenta have a high metabolic rate, especially in early intra-uterine life. Therefore they can successfully compete with maternal organs for nutrients in the blood stream. If in food shortage there is a depletion, then the placenta, with its high basal metabolic rate successfully obtains its requirements, whereas adipose tissue at the other extreme not only fails to obtain its limited requirements but, owing to the low control of the blood stream, loses weight. This would happen by a reversal of the normal chemical equation of synthesis in accordance with the Law of Mass Action. This hypothesis will explain why in iron shortage, protein shortage, salt or vitamin deficiency in pregnancy dietaries, when there is competition between the mother and child, there is born a healthy child without anaemia, of full weight, and of good calcification, from a mother who is anaemic, poor in weight, with defective teeth, or osteomalacia acquired during pregnancy. Dietary supplementation is therefore indicated. Further, in moderate deficiencies the child will be short of stored material and will run out of stores before lactation is ended, especially of iron, and so have a lowered resistance to infection. In this connexion one can refer to the long series of publications from the school of Parsons in Birmingham, the work of McKay and Goodfellow (1931), and of Strauss (1933); all are now of classical importance. Iron supplementation of the diet is essential for the mother on a normal diet, and becomes essential for the foetus also if rations are grossly depleted.

PREMATURITY AND IMMATURITY. Wallace (1948), working with Hammond, showed that in pregnant sheep (full term 150 days) at 91 days diet had little influence on different organs or on the foetus as a whole, but after that date until full term a high protein and vitamin diet resulted in well-formed lambs and vice-versa. His results are shown in Table 1 and in Fig. 4. After four weeks on a maintenance diet, six pregnant ewes were put on a low diet giving loss of maternal weight, and six on a high diet giving ample supplies and gain of weight. At the fourteenth week three of each group exchanged dietaries until full term. At term it was clear that the diet in the first 13 weeks had little effect on the lamb, but the diet in the last eight weeks was the determining factor. Further, it increased the milk yield immensely. The high diet yielded a high birth weight, high milk yield, good lamb growth, and zero neonatal mortality. Further, the low dietary lambs had a retarded physiological development of the

TABLE 1

INFLUENCE OF HIGH AND LOW PLANE DIETS IN LAST EIGHT WEEKS OF PREGNANCY ON BIRTH WEIGHT AND POST-NATAL GROWTH (WALLACE, 1944 AND 1946)

Diet	High Plane	Low Plane
Effect on ewe weight (lb.) ..	44 gain	11 loss
Birth weight (lb.)	10·4	6·8
Milk yield in third week (lb.) ..	50	30
Milk yield over 16 weeks (lb.)	443	292
Lamb weight at 16 weeks (lb.) ..	72	56
Temperature control at birth ..	Present	Absent
Neonatal mortality	Nil	High

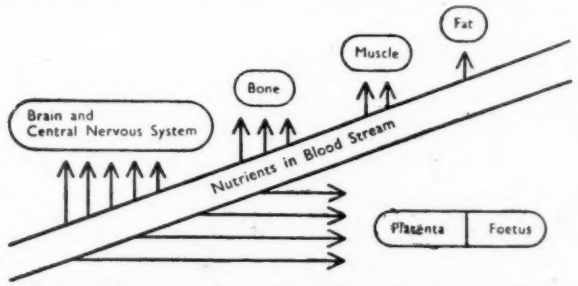


FIG. 3.—Diagram of priority of partition of nutrients according to metabolic rates. The demand for nutrients by an organ varies as the number of arrows shows. Shortage in the blood stream means that those tissues with the lower demand fail to compete with those with higher demand and stop growing or may even lose weight (Hammond, 1944).

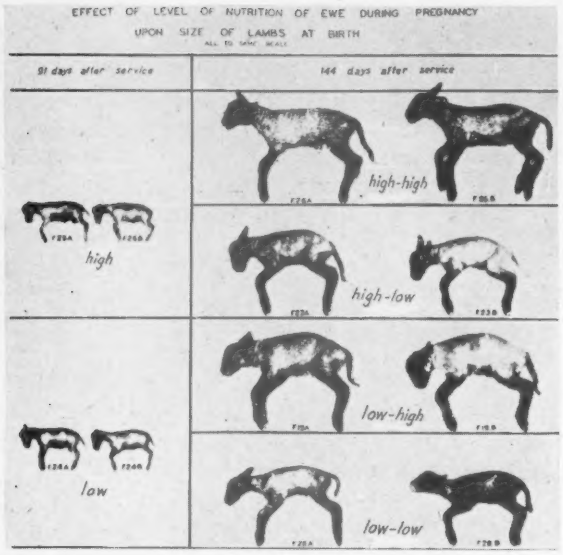


FIG. 4.—Level of nutrition of ewe during pregnancy upon size of lambs at birth (Wallace, 1948). Two series of ewes fed on low rations and high rations to 91st day of pregnancy respectively. Each series was then divided, half being put on high and half on low plane of diet or rations.

temperature control mechanism at birth, and this would contribute to a high neonatal mortality.

These facts explain the points brought out by Illingworth, Harvey, and Gin (1949), that poor birth weight is effective for many years after birth in contributing to retarded development, despite the views of Hess and Chamberlain (1927).

The crucial thing is that each organ has its specific date of optimum growth according to the pattern of development. At that date, whether prenatal or postnatal, it needs ample supplies of foodstuffs. If each organ does not obtain them at that time, it is a poor substitute to give them later, since they cannot be usefully used by an already formed organ, but are utilized by other organs whose specific date of optimum growth coincides with the accretion of foodstuffs. A child who was fed on poor food supplied in early life has a light skeleton and a poor musculature, and does not restore these by 'feeding up' in those years after the dates for building skeleton and muscle. What is good for the child is also true for the foetus.

Mechanism of Action

There are three major factors of intra-uterine origin influencing the health of the child: the genetic, the placental, and the foetal. The first will not be now considered, but the other two groups repay attention.

Placental Factors

Placental Morphology. It was shown by Grosser (1925) and by Mossman (1937) that histologically the placentas of mammals can be grouped in four classes according to the number of layers intervening between the maternal and foetal bloods at full term. All begin with six layers: the maternal endothelium, the uterine connective tissue ('syndesmium'), the maternal uterine epithelium (endometrium), the foetal chorionic epithelium and syncytium, the foetal villous connective tissue and the foetal endothelium of the villous blood vessels. As the placenta grows in different types it loses varying numbers of the intervening layers, so that in the human placenta we have a haemo-chorial placenta at term; that is, maternal blood is in direct contact with the chorion of the villi. In the rabbit, some of the chorion goes and we get a haemo-endothelial placenta; in the dog there is an endothelio-chorial; in the ungulata, a syndesmo-chorial; and in the pig, an epithelio-chorial placenta, in which no tissue at all disappears.

FIG. 5.—Diagram illustrating the Grosser-Mossman classification of placentas. The black spots represent foetal corpuscles and the rings the maternal corpuscles, each enclosed in their vascular endothelia. The progressive approximation of the blood streams in the last stages of the four main types of placenta is shown.

Placental Diffusion. The view is that the placental diffusibility bears an approximate relation to the number of intervening layers. This is, it appears, true for inorganic crystalloids as shown in the beautiful work of Flexner and his colleagues (1942) with isotopes on the permeability of different types of placentas to water and sodium chloride in which

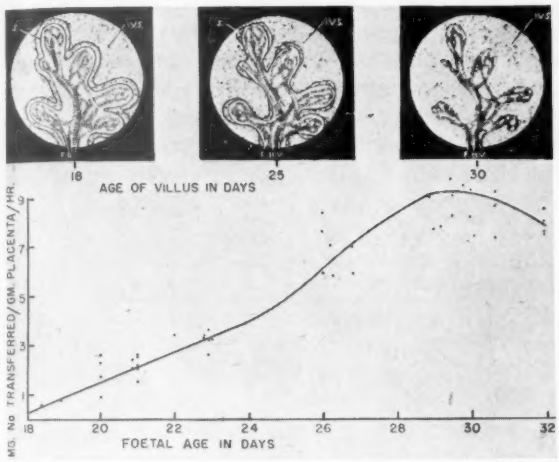


FIG. 6.—The permeability of the rabbit's placenta to Na^{23} at different foetal ages correlated with the villous structure (Flexner and Gellhorn, 1942).

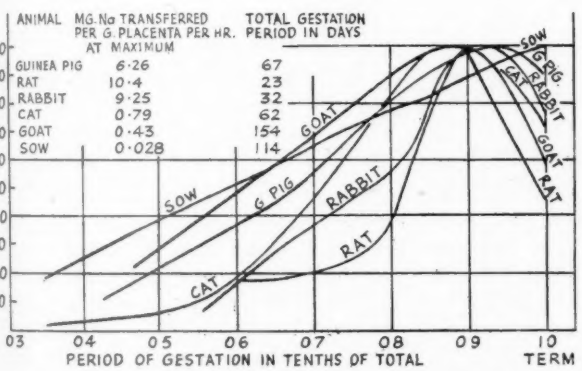


FIG. 7.—The permeability of placentae of different Grosser-Mossman groups to Na^{23}. The increase in permeability in late pregnancy occurring with approximation of the blood streams in the rodents on the one hand, and uniformity of permeability through pregnancy in the sow at the extreme is shown (Flexner and Gellhorn, 1942).

he used heavy water or sodium chloride with Na^{23} as the isotope. We see well how the passage increases in the late months. It is also in some degree shown for some colloids, e.g. antibodies, as we see in Rodolfo's work (1934) on the passage of antibodies across the placenta of the rabbit.

Water may pass by diffusion but there are problems which cannot usefully be discussed here. However, sodium chloride, oxygen and carbon dioxide appear to diffuse across under pressure in all types and to be reversible if the gradient is reversed. Asphyxiation of the pregnant ewe under caesarean section results in carbon dioxide going back to the foetus (Huggett, 1927). This reversibility rules out active placental gaseous secretion. Roughly speaking, molecules under 350 molecular weight appear to diffuse (Anselmino, 1929). There are, however, important exceptions, both in placental types and in individual substances, so important

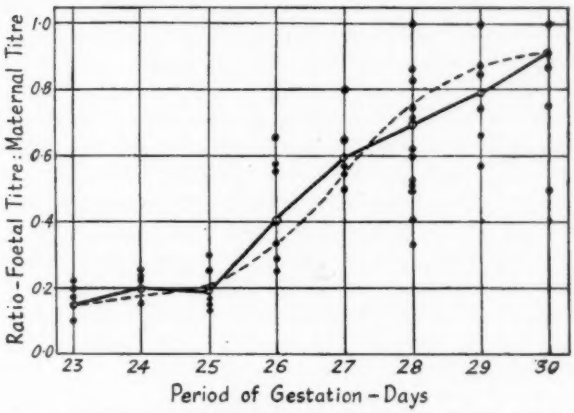


FIG. 8.—Permeability of the rabbit's placenta to antibodies at different times during prenatal life (Rodolfo, 1934).

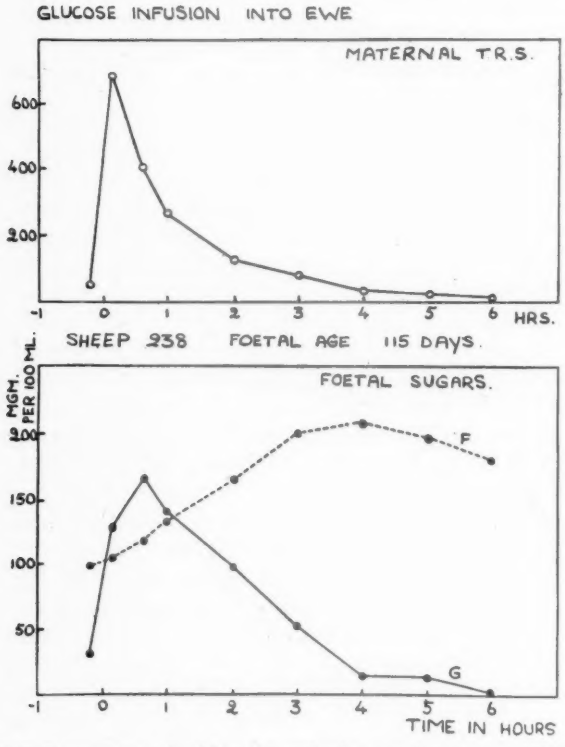
that we must consider the possibility of active placental intervention, secretion or vital activity as a factor in transfusion.

Active Placental Intervention. The evidence for this is profuse. It rests on the staining of the placenta in man and other animals. Perhaps the best description is that given by Wislocki and his colleagues at Harvard, who have shown, to take three instances, that the human placenta contains considerable amounts of stainable enzymes, notably phosphatases (Dempsey and Wislocki, 1947), which we know to be active in the metabolism of fats and carbohydrates: it also has two types of stainable iron, that interpreted as being in association with oxidative enzymes (which often contain iron), and that identified as transport iron (Dempsey and Wislocki, 1944). Finally, it is possible to identify histologically materials in association with the staining reactions of steroid hormones (Wislocki and Bennett, 1943) such as oestrone and progesterone which are known to be secreted by the placenta into the mother. In other words, the placenta, unlike the capsular membrane of the kidney or the lung epithelium, has materials which would probably be

redundant if simple diffusion were the sole transport mechanism. It is possible to illustrate this fact by a consideration of certain specific materials.

LIPOIDS. Popják (1947) gave potassium phosphate labelled with radioactive phosphorus, P^{32}, to pregnant rabbits and later extracted the phospholipids from the maternal blood, the placenta, the foetal blood, and the foetal liver. He then estimated the amounts of P^{32} in the four purified phospholipids. He showed that there was more in the placental fraction than in either of the two blood fractions. Therefore there must have been a fresh synthesis of lipoids in the placenta, otherwise, if mere storage had occurred, there would have been identical amounts of P^{32} in each fraction. Also, since the foetal blood lipid had a third and lower content of P^{32} it could not have been formed by mere diffusion, but must have been made by an active chemical katabolic process in the placenta. That is, active secretion and not diffusion was the mechanism. Similar reasoning showed that lipid concentration in the foetal liver was active and not passive.

CARBOHYDRATES. Again, if glucose be injected into the maternal or foetal blood of the sheep, it appears on the other side very rapidly (Huggett, Warren, and Winterton, 1949). But at the same time there is a slow, long-continuing rise in the blood of a second sugar normally present in sheep foetuses, namely fructose. The total concentrations will exceed in the foetus the maternal glucose. In a case of viable twins, we found that if one was separated immediately after birth, but the cord of the second left intact with its umbilical circulation, there was a distinct difference. Though both twins had been injected with the same amount of glucose, the second only formed fructose, showing that it is made by the placenta and not by the foetus itself from glucose. Further, fructose normally disappears from the lamb within 24 hours of birth (Cole and Hitchcock, 1947).



T.R.S.=maternal blood reducing substance (99% glucose). F.=*foetal blood fructose.*

FIG. 9.—Chart of the passage of glucose across the placenta of the sheep and formation of fructose.

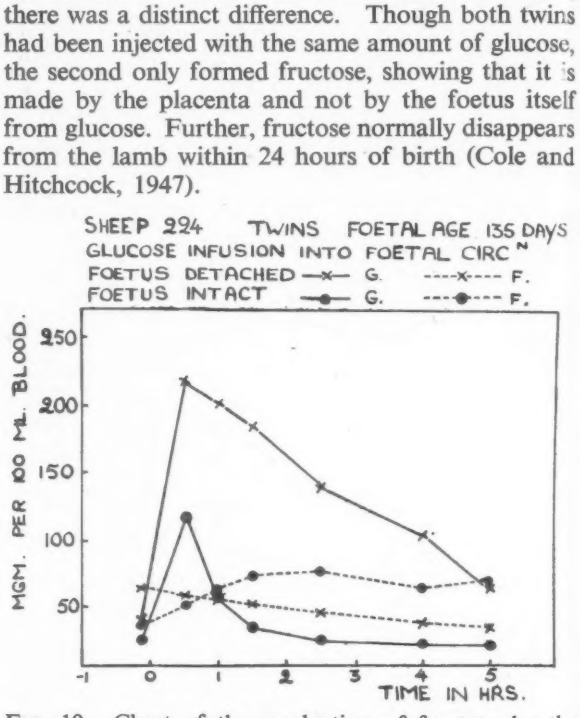


FIG. 10.—Chart of the production of fructose by the placenta but not by the foetus. Glucose infused into twin foetuses during caesarian section. One umbilical cord then cut and foetus detached, other left attached. Fructose only found in second case but steadily disappeared in detached foetus.

It is clear, therefore, that the placenta passes sugar across by two mechanisms, one probably by simple diffusion and the other by an active transmutation into fructose.

Of practical importance to this question and to those interested in human physiology, is the relation of the mechanism of fructose production to fructosuria in man. Here it is important to note two things: first that this is a rare condition, and secondly, that neither we nor Karvonen (1949) have been able with the best modern techniques to confirm the presence of fructose in human foetal blood as described by Orr in 1922. It is present only in certain species of mammalian embryos. Also, concerning the passage of sugars we know that human and rodent placentae contain considerable amounts of glycogen which is very stable and

independent of the maternal blood stream. The function of glycogen is unknown: in fact, at the moment, the more we know about it the less certain we are of its interpretation (Huggett, 1929; Davey and Huggett, 1932; Dempsey and Wislocki, 1944; Wislocki, Deane, and Dempsey, 1946). The occasional presence of fructose in adults is a clinical problem remaining to be solved, but one which, we feel, is being opened up, particularly by the work of Mann and his colleagues at Cambridge, who have shown that it is present in seminal fluid, secreted by the seminal vesicles under androgenic control, and utilized aerobically by spermatozoa (Mann, 1946; Davies and Mann, 1947; Mann and Parsons, 1947). It is of interest to note that fructose is always found associated with the foetus or the reproductive tract.

PROTEINS. There is evidence that nutritional quantities of proteins probably pass by amino acid diffusion under appropriate pressure gradients. But the whole problem of the Rh factor has led to our recasting our ideas about protein passage, and, further, the disorders of childhood for which it is apparently responsible, are multiplying annually.

It is now clear that, while antigens pass across hardly at all, antibodies pass with relative ease. But only about 50% of human placentas are permeable to the passage of the Rh antibody from a Rh-negative mother back to the Rh-positive foetus (Hughes, 1949). This differential permeability has been predicted by Haldane (1942), and there appears some evidence of a biological variation in the permeability of the placenta (Dienst, 1905). On the other hand, while antibodies in the maternal blood normally pass the placenta, Hartley (1949) has shown that there is a peculiar selectivity present in this organ. A woman with diphtheria at the end of her pregnancy received purified antitoxin. It was assumed that the twins she carried would be immunized. Nevertheless, they developed diphtheria after birth and one died. It was found that crude antiserum and precipitated globulin passed the placenta, but purified detoxicated antiserum did not traverse. The placenta, therefore, has a selective action, since larger molecules passed across but smaller ones were excluded. It is important here to refer to the work of Brambell and his colleagues in north Wales. They have shown that in the wild rabbit (whose placenta is histologically a shade more permeable than the human) maternal proteins enter the foetus and kill a percentage of a litter by fibrin formation (Brambell and Mill, 1947).

There is no point in referring here to the rôle of the placenta as a ductless gland controlling maternal metabolism in pregnancy. The theme has been beautifully developed by Professor William Newton of Edinburgh in some of the most finished examples of scientific method in this generation of scientists.

Our new problem therefore is, To what extent are the functions and development of the placenta under our control? There is, I am glad to say, some hopeful evidence, since it is possible to alter its morphology (Huggett and Pritchard, 1945; Pritchard and Huggett, 1947; Popják, 1946).

Foetal Factors

Foetal antenatal functions can be divided into those which continue into post-natal life with no abrupt change, and those which have such a change. Taking the second group first, we can list them as: (1) Closure of the umbilical circulation, the ductus venosus, and the hypogastric arteries; (2) closure of the foramen ovale and the ductus arteriosus, with opening of the pulmonary circulation, this occurring first; (3) the volume of circulatory blood; (4) cessation of placental transmission and the onset of alimentary and full renal function; (5) fall of external temperature, and therefore the task of constant temperature control (successful in the plantigrade newborn, such as lamb and foal, but inadequate in human newborn); (6) sensory stimulation of the skin on a new scale and distribution; (7) a changed pattern of growth with different rates for different organs.

Among the functions which, so far as we know, undergo no abrupt change, we can include motor function and control by the brain and cord, apart from responses to new stimuli. Further, there is the growth of the metabolic functions which are accompanied by a steady fall in the metabolic rate. In addition, there is the growth with the total neuromuscular mechanism of the control of temperature which, however, does not reach full function until some months after birth. The newborn infant is, like the amphibian, a cold-blooded animal.

Quite clearly the more premature an infant or the more immature it may be, due to malnutrition of the mother, the more it will lack development of these functions. It is therefore of the utmost urgency to maintain the maternal nutrition in pregnancy optimal in quantity and quality. It is pertinent here, however, to refer to the beautiful and finished research of two united teams of workers in this branch of physiology. Oxford and Cambridge, at the instigation of the late Sir Joseph Barcroft, joined forces in the personalities of Barcroft, the late Alfred Barclay and Kenneth Franklin, now at St. Bartholomew's, ably assisted by many colleagues, especially from the United States. They brought light into intra-uterine and neonatal darkness, often the short wave light of x-rays, but they clarified the situation and elucidated

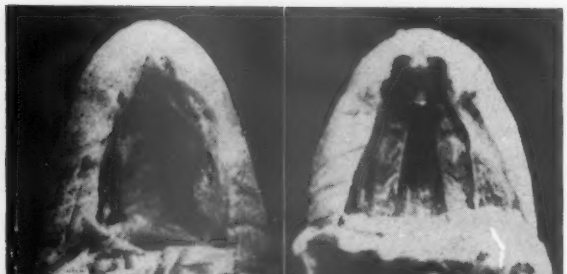


FIG. 11.—The palates of two rats, A and B, at birth. Rat B was born with a cleft palate from a mother kept on a riboflavin-free diet during pregnancy. Rat A was a normal control (Warkany, Nelson, and Schraffenberger, 1943).

the physiology of a region which Blalock has transmitted into practical surgery for the infant.

Concerning the functions which undergo the abrupt change, I would speak of three. You are all aware of the finished and lucid work on the kidney of the newborn by Professor R. A. McCance and his colleagues. He has told you of it. It must be confessed that we know little of renal function before birth, but it is quite clear from his results and from the histology of the glomerulus, that it is adequate but imperfect, has little concentrating power, and possesses a salt intolerance, if one may use the term.

My former colleague, David Greenfield, now professor of physiology at Belfast, and Keith Cooper, now with the Royal Air Force, turned from studying the blood flow in the brain when subjected to big gravitational forces, to the blood flow in the umbilical cord. By enclosing the sheep foetus in a saline-filled box (a plethysmograph) without injuring or disturbing the umbilical cord, they were able to apply sudden pressures sufficient to stop the venous flow back to the foetus but not to stop the arterial flow out. Thus the foetus shrank as the outward blood flow to the placenta continued unchanged. As a result the rate of flow through the placenta was measured (Cooper and Greenfield, 1949; Greenfield, 1949; Cooper, Greenfield, and Huggett, 1949). This measurement by Greenfield and Cooper has laid the foundation of an accurate knowledge of the cardiac output and of the foetal metabolism. Correlated with oxygen and nutrient contents we are enabled to obtain clearer pictures of foetal metabolism than ever before (Cooper, Greenfield, and Huggett, 1949).

We have discussed a pattern of growth, the role of the placenta in transmitting nutrition, and the power put into our hands by Greenfield to measure total metabolism. In 1921, Zilva, Golding, Drummond, and Coward showed that absence of vitamin A in the diet of pregnant animals caused congenital cataract. This was forgotten until the last war when simultaneously Gregg in Australia (1941) and Warkany in the U.S.A. described congenital defects. Gregg's discovery, as is well known, was in infants born of mothers who in pregnancy between the restricted period of the fifth and eighth weeks were ill with German measles. Warkany and Nelson (1941), in a series of papers beginning in 1941, showed that pregnant rats on a riboflavin-deficient diet delivered themselves of litters with bone and thyroid defects, provided that the diet deficiency was before the thirteenth day. It would appear that the rubella virus (if we may so call the active agent) can attack enzyme systems actively engaged in optic lens formation and heart formation. When these tissues are formed other enzyme systems are not so attacked; similarly, vitamin A and riboflavin are essential as catalyst

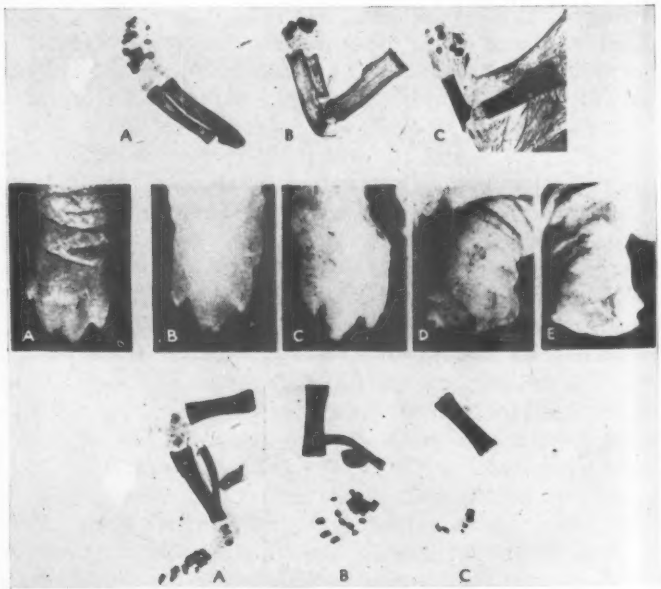


FIG. 12.—Three figures illustrating the progressive loss of bones and digits in rats at full term when delivered from mothers maintained on diets of varying shortage of riboflavin. The absence of digits in the paw is shown and also the fusion of small bones or complete absence of ossification in bony centres (Warkany and Nelson, 1941).

for lens or bone-forming enzyme systems, but not for enzyme functioning in the formation of other organs.

Finally, I would close by referring to the work of Dr. Kenneth Cross which, like Greenfield's, exemplifies the value of accurate work allied to modern precision methods. He has addressed himself to the basic physiology underlying respiration and foetal apnoea. Haldane in 1904 showed us the rôle of gases in controlling the respiratory centre. Cross (1949) has attempted this evaluation in the infant and finds that the physiology is not the same as in the adult: that is, it may be possible that once again we are dealing with an imperfectly formed function which must, like all others, be assessed for the infant and child by standards different from the adult if we are to make good progress in treating our children.

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STUDIES IN ANAEMIA OF INFANCY AND CHILDHOOD*

THE HAEMOGLOBIN, RED CELL COUNT, AND PACKED CELL VOLUME OF NORMAL ENGLISH INFANTS DURING THE FIRST YEAR OF LIFE

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(Received for Publication, August 18, 1949)

The difficulty in establishing a normal standard for the blood picture in infancy is emphasized by the wide range in values recorded by different workers on this subject. Such variations may be due in early work to differences in technique and in later work to the use of different criteria of normality in infancy, to the random selection of infants and the acceptance of such as normals, to racial differences, and to the limitations imposed by a haemoglobin estimation without a corresponding red cell count.

The present work was planned in an attempt to establish normal values for English infants, to account for the disparity between the findings of different workers, and to determine whether all infants should receive prophylactic doses of iron in their first year of life.

Choice of Sample

In the present investigation the term 'normal' was used in a restricted sense and was applied only to those infants who, besides being 'standard' or 'average' and apparently healthy on physical examination, were not subjected to influences likely to produce anaemia during the first year of life. Thus, when infants were being selected for a normal series, those were excluded who were premature, immature at birth, one of a multiple birth, or who weighed less than a minimum of 6 lb. at birth. Also excluded were those who had suffered from any neonatal disease or from any infection during the first year of life.

It was considered necessary to exclude the children of anaemic mothers, although anaemia in the mother during pregnancy does not invariably lead to anaemia in the child. Mackay and Goodfellow (1931) could find no difference between the haemoglobin levels of infants born of anaemic mothers and of those whose mothers were given protective doses of iron; Strauss (1933), who examined a small number of infants of severely anaemic and of healthy mothers, found a statistical difference between the haemoglobin levels in the two groups and states that 'infants born to mothers suffering from iron deficiency, although exhibiting at birth a normal blood picture, are unable to maintain a normal haemoglobin level during the first year of life.' Parsons (1932) and Parsons and Hickmans (1933) have described the occurrence of congenital nutritional anaemia in infants born to women suffering from an iron deficiency anaemia. Since such infants are a possible source of error, they should not be included in any 'normal' group.

An adequate supply of iron in the diet is essential for the maintenance of a normal blood picture at any age; during infancy, as cows' milk contains less iron than breast milk, the substitution of cows' milk mixtures for breast milk is likely to be detrimental to the child. Prolonged nursing or prolonged cows' milk feeding to the exclusion of a mixed diet must also be avoided. A hypochromic anaemia following such milk diets has long been known and has been given the names of 'milk anaemia' and nutritional anaemia of infants. This anaemia must be prevented in any normal series by the early addition to the infants' diets of foods containing iron and by avoiding any delay in weaning. In the present series breast-feeding was carried out for at least six months, additions to the diet were started at five to six months, and weaning was completed by nine months.

One indication of health in infancy is an average gain in weight: any infant more than 10% below the average weight for its age and birth weight

* The investigations described in this paper were carried out in the years 1937-1939 under the direction of Sir Leonard Parsons, but publication of the results has not hitherto been possible.

should be excluded from a normal series. Although not of itself abnormal, a rapid rate of growth has been recognized as a factor in the production of anaemia in infancy. For instance, in the statistical analysis made by Bradford Hill of Mackay's figures (1933) it was found that from six to twelve months of age the haemoglobin level was correlated with the rate of growth; that babies who made the largest percentage increase in weight over their birth weight tended to have the lowest haemoglobin levels. In the majority of investigations into the normal blood picture in infancy insufficient stress has been laid on this point and it is possible that some anaemic infants may thus have become included in a normal series. The rapidly growing, premature infant frequently develops in the second half-year of its life a low haemoglobin level which, because of its grossness, has been recognized as abnormal; on the other hand, finer shades of anaemia have been overlooked in the small, full-term infant who achieves the average weight for all infants at the end of one year. Thus, like premature infants, small infants, who may be expected to double and treble their birth weight much earlier than large infants, are potential sources of error. In the present investigation infants weighing less than 6 lb. at birth were therefore excluded. It is also possible that the big, breast-fed baby who at one year weighs much more than the average for its birth weight is also suffering from a borderline anaemia similar to that of the rapidly growing small baby. Therefore any large full-term infant of excessive weight at one year of age is another possible source of error and should be excluded from the group of normal infants. In the present series one breast-fed infant was excluded on this account.

In spite of every care being taken to select a normal sample of the infant population there will probably still be some babies who will develop mild hypochromic anaemia without any obvious cause (Guest and Brown, 1936). This hypochromic anaemia, together with that due to known causes at this age, has received the name nutritional anaemia of infancy, the material lacking being ultimately iron, the demand exceeding its supply, and the condition being easily cured by giving suitable doses of iron for several weeks. The anaemia usually remains unrecognized in its early stages and therefore the average blood picture of a group of healthy and apparently normal infants is likely to fall below that of a similar group of infants protected from such a nutritional anaemia by adequate doses of iron (Mackay and Goodfellow, 1934). As the administration of iron, a recognized therapeutic procedure, improves the blood picture in the unprotected groups of infants, this group should probably be regarded as subnormal and the iron-fed group should not be regarded as 'artificial,' 'supernormal,' or 'abnormal.' The iron-fed group may instead be considered an 'ideal' normal and its blood counts may be compared and contrasted with those of the normal series of infants. In the present investigation such a comparison was made in infants of 12 months of age.

The lack of recognition of borderline cases of anaemia in infancy has been partly due to the custom of obtaining an average picture of the haemoglobin changes in infancy by examining cross-sections of the infant population at different ages. This method obscures any finer changes occurring in individual cases, and although the general trend of the blood count in infancy is represented, such an average gives no indication of the limits of normal at any particular age. Repeated examinations in one individual are of more value in determining the change and limits of normal than are those made at random on a number of individuals. In the present work both methods were used: one group of infants was followed from birth to one year of age, and a second group of infants, examined on a few occasions only, was used in the determination of the average.

Guest and Brown (1936) found that borderline cases of anaemia occurred more often than is commonly realized. This is due to the reliance placed by many investigators on the haemoglobin level alone as an index of anaemia. Guest and Brown state that in the development of nutritional anaemia diminution in the size of the red cells occurs before the fall in haemoglobin level, but that the two changes are additive and both depress the mean content of haemoglobin per cell. They consider that a haemoglobin content of 20 $\gamma\gamma$ or less per cell justifies a diagnosis of anaemia whatever the total haemoglobin. Parsons, Hickmans, and Finch (1937) have shown that the earliest signs of an iron deficiency anaemia in rats are polycythaemia and microcytosis with a normal haemoglobin value. Therefore in order to obtain a complete blood picture it is necessary to correlate the haemoglobin with the red cell count and measure the packed cell volume. This was done in the present investigation.

Review of the Literature

Since the end of the last century numerous studies of the blood picture during infancy have been made, and by 1916 a broad outline had been obtained. It was then known that at birth the haemoglobin level and the red cell count were high compared with adult figures and that they became relatively

lower in the second half-year of life. In that year Williamson of Chicago published figures for the haemoglobin level from birth to old age. Using blood obtained from the pulp of the finger he found the average haemoglobin level at birth to be 23·4 g. per 100 ml. of blood, and in the first year of life to be never less than 12·5 g. haemoglobin per 100 ml. of blood (Table 1 and Fig. 1). This is a consistently high level compared with that of most later work, and as Williamson does not mention the minimum birth weight in his series, it may be an erroneously high level. His work has been criticized because of the standard of recrystallized haemoglobin which he used but, as Mugrage and Andresen (1936) point out, ' His values may be high but the general nature of the curve he obtained is significant.' In support of his figures are the findings of Merritt and Davidson (1933) and of Faxen (1937), which were obtained at monthly intervals from birth and which closely parallel Williamson's figures (Table 1).

In 1918 Appleton, using the method of Palmer and Van Slyke and examining blood from the capillary circulation, determined the haemoglobin level in 103 New York children from birth to two years. Appleton does not mention the birth weights of the children he examined but all appeared healthy and 90% were breast-fed. The curve of haemoglobin averages followed that of Williamson's cases, the absolute amount at birth being 22·6 g. %, but in the latter half of the year falling below Williamson's figures to 12·0 g. % and corresponding closely to that of the majority of later workers (Table 1). It should be noted that Appleton placed all children of ages 6 to 11 months in one age-group

TABLE 1
HAEMOGLOBIN VALUES (%) IN INFANCY AS RECORDED BY VARIOUS AUTHORS

Age	Williamson	Appleton	Drucker	Mackay	Elvehjem	Merritt and Davidson	Mugrage and Andresen	Faxen	Present Author
0–48 hours	169	164		143	160	169	125	168	148
3– 7 days	160	135						169	141
8–21 ,,	155	137	123	130	130		120		130
22–35 ,,	133	102	99	106		118		130	110
6– 8 weeks			87	88	97	95		98	96
9–12 ,,			79	74	84		80		86
13–16 ,,	99	88		77	86	91		92	87
17–20 ,,			83	81	87	93		97	91
21–24 ,,				86	88	94		99	89
25–28 ,,				86	86	95	89	97	90
29–32 ,,		87		86	84	94		94	88
33–36 ,,	99		81	86	86	92		96	86
37–40 ,,				86	83	94		95	86
41–44 ,,				86	82	94	86	96	85
45–48 ,,			80	86	83	91		93	82
49–52 ,,	91	85		86	84	90		97	90
53–56 ,,		to 23 months	84 to 2 years	86	83		85 to 18 months		84

100% = 13·8 g. haemoglobin per 100 ml. blood.

and all of 11 to 23 months in another age-group. The inclusion of such a wide range of ages in each group may have produced a false picture of the haemoglobin level as it is from the sixth month onwards that nutritional anaemia is most likely to develop and finer changes that might occur at this time will not be detected by such grouping.

In 1923 and 1924 Drucker investigated methods of obtaining blood from infants and estimated the haemoglobin content and red cell volume in 85 healthy Danish infants aged from two weeks to two years. He found that what had been described by various authors as physiological variations in the haemoglobin level of infants were due to faulty technique. Thus, variations described as being due to the site of the puncture, the time of day, the relationship to meals, and so on, could be abolished by the use of an extremely sharp instrument, in his case a razor. Twenty-eight of these infants were breast-fed and Drucker found no differences between breast-fed and bottle-fed babies nor any between the sexes at this age. The youngest infants he examined were two to three weeks old, and at this age the haemoglobin level was 17·0 g. per 100 ml. of blood. In his cases the lowest haemoglobin level was found between 8 and 12 weeks of age and was 10·9 g. %. It then rose between three and six months to 11·5 g., fell to 11 g. between 9 and 12 months and rose again to 11·6 g. during the second year (Table 1). In this second rise, slight though it is, his figures correspond to those of Monrad and Ormu (quoted by Drucker) obtained in Danish children and are in contrast to Williamson's and Appleton's figures for American children which showed their lowest value in the second year. Unfortunately, Drucker did not make red cell counts in these infants but the figures for cell volume he found at their lowest at 8 to 12 weeks of age, that is, at the same time as the haemoglobin, and that, like the haemoglobin, they rose gradually during the following months.

In 1931 Mackay and Goodfellow published the results of several years' work on the haemoglobin level of London infants from birth to 14 months of age. These figures were revised in 1933. The infants weighed from $5\frac{1}{4}$ to $9\frac{3}{4}$ lb. at birth and were placed in three groups. The first group consisted of infants who were breast-fed up to the age of three months, and after that age consisted of infants who were being given prophylactic doses of iron. This group Mackay called 'normal,' and using the method of Haldane found the haemoglobin to be 19·7 g. % at birth, 10·2 at two to three months, and from approximately five months of age to be 11·8 g. per 100 ml. of blood. Mackay's second group consisted of breast-fed infants who were not treated with iron. The same low haemoglobin level was found at two to three months in these cases, and there was then a rise from four to eight months to 10·8 g. % followed by a slight fall to 10·4 g. at 9 to 13 months. This rise at four to eight months is similar but not as great as in the first group and is followed by a fall not seen at all in the first group. The third group comprised untreated bottle-fed infants who showed a similar but greater divergence from the normal group. At two to three months of age their haemoglobin level was 9·5 g. %. These three groups all included infants of between 5 and 6 lb. birth weight. Such cases, like premature infants, might well influence adversely any average haemoglobin values. In the first group the prophylactic use of iron should have prevented any fall of haemoglobin due to this factor. It is possible that this effect was produced in the second and third groups: hypochromic anaemia may have been present in some cases and, the haemoglobin value being regarded as a low normal, have escaped detection. Mackay did not make any corresponding red cell counts in her cases; had she done so, cases such as those described above as 'low normals' might have been recognized as masked cases of anaemia. Mackay's group of breast-fed infants given iron showed average haemoglobin values lying at a much lower level than those of Williamson's cases but approximating to those of Drucker in the first six months and to those of Appleton in the second six months of life (Table 1 and Fig. 1).

In 1933 Elvehjem and his co-workers, using a Bausch and Lomb colorimeter, studied the capillary blood of 720 white children up to five years of age in Madison, U.S.A. They excluded from their series premature infants, twins, anaemic children, and those having treatment, but they made no

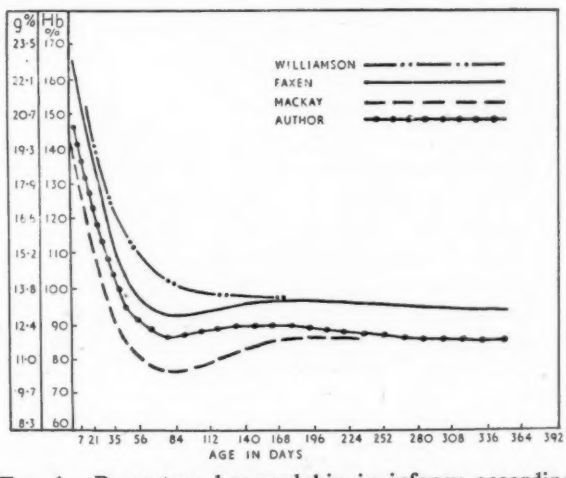

FIG. 1.—Percentage haemoglobin in infancy according to various authors.

mention of the minimum birth weight in the series. Their results followed the usual trend and the haemoglobin values lay between the lower ones of Mackay and the higher ones of Williamson. At birth the haemoglobin value was 22·2 g. %, at 8 to 12 weeks 11·9 g., and during the remainder of the year it altered only slightly (Table 1). In 1935 they published results in a similar age-group of children who had been given iron and copper by mouth. They found that the characteristic fall of haemoglobin in the first few months still occurred but in the later months the haemoglobin levels were all higher than in the previous series. They concluded that between three months and one year of age the haemoglobin level should lie between 12 and 13·5 g. per 100 ml. of blood and that 'the fact that the values for practically all the untreated infants are lower than the values obtained after therapy forces them to conclude that a large number of children suffer from slight anaemia.' Unfortunately both of their investigations suffered from the same defect as Mackay's work in that there were no red cell counts with which to correlate the haemoglobin findings. Elvehjem and his colleagues agree with Mackay that there is a difference between the haemoglobin values of a group of infants to whom iron is given and one from whom iron is withheld, but neither he nor Mackay has enough data to show in what way this difference develops.

In 1933 Merritt and Davidson, using a modification of Wong's method of estimating haemoglobin and making corresponding counts of the red cells, attempted to follow from birth to one year 73 healthy American infants. Success was achieved in 15 cases and these were examined at monthly intervals throughout the year. The infants were full-term but the minimum birth weight was not stated; they were healthy, mostly breast-fed, and were drawn from a poor and unprivileged population of mixed racial origin. Blood was obtained by puncturing the toe with a Hagedorn needle. The authors do not show findings in individual cases but show maximum, minimum, and mean values in monthly age-groups throughout the year. Although their average was much higher than in Mackay's cases and lay close to that of Williamson, the difference between maximum and minimum counts at each age-period was great. After the high initial value of 23·4 g. of haemoglobin at birth they found that, beginning with the fourth month, the greater number of infants had haemoglobin levels between 13 and 14·9 g. % except in the ninth and twelfth months when the greater percentage lay between 11 and 12·9 g. % (Table 1). The red cell count fell from a mean at birth of 5·95 million per c.mm. to 4·74 million at the second month and thereafter made only minor fluctuations (Table 2). From the second month onwards the majority of values fell between 4·5 and 4·9 million cells per c.mm. and from the fifth to the eighth month there was 'a dispersion of values suggesting a lability of erythocyte level under the influence of environmental factors.' In this way they noted some alteration in the relationship between red cell counts and haemoglobin values but did not show in what way that relationship was changing. It was left to Guest and Brown (1936) to point to the explanation of this change though not to demonstrate its occurrence in apparently healthy children.

TABLE 2
RED BLOOD CORPUSCLES (MILLIONS PER C.MM.) IN INFANCY ACCORDING TO VARIOUS AUTHORS

Age	Merritt and Davidson	Mugrage and Andresen	Faxen	Present Author
0–48 hours	5·95	4·86	5·78	6·54
3– 7 days		4·22	5·47	6·30
8–21 ,,				5·85
22–35 ,,	5·19		4·70	5·02
6– 8 weeks	4·74		3·91	4·53
9–12 ,,		3·90		4·14
13–16 ,,	4·65		3·96	4·42
17–20 ,,	4·61	4·23	4·20	4·91
21–24 ,,	4·67		4·46	5·03
25–28 ,,	4·73		4·57	5·14
29–32 ,,	4·70		4·30	5·07
33–36 ,,	4·65	4·28	4·41	4·72
37–40 ,,	4·79		4·43	5·23
41–44 ,,	4·74		4·45	5·17
45–48 ,,	4·70		4·53	4·96
49–52 ,,	4·67		4·58	5·33
53–56 ,,		4·25 to 18 months		5·41

In 1936 Guest and Brown of Cincinnati stated that nutritional anaemia might be seen not only in milk-fed infants but also in infants who had been offered a seemingly well-balanced diet. This anaemia was found to improve with a better diet in the case of milk-fed infants or spontaneously in those on a good mixed diet. Nevertheless, they say, the period of transition is a critical one for the infant. Guest and Brown showed that in the development of nutritional anaemia in infants 'diminution in the size of the cells occurs earlier than the decrease in the haemoglobin concentration but the two changes are additive and both depress the mean haemoglobin

content per cell.' In anaemic infants they found that with a low haemoglobin level, microcytosis and hypochromia, the red cell count might be normal, low or high. They state that a 'haemoglobin content' of 20 $\gamma\gamma$ or less per cell justifies the diagnosis of anaemia whatever the total haemoglobin; in some cases the haemoglobin level might be as high as 11 g.% yet it would be found that iron medication produced an improvement in the total blood picture. The fact that anaemia might be present with a normal, a low, or a high red cell count helps to explain the wider dispersion about the mean of the red cell values in Merritt and Davidson's series from the fifth to the eighth month. In other words it is probable that there were included in Merritt and Davidson's series some infants who were actually developing a mild anaemia but in whom such changes were not gross enough to warrant their exclusion from the series. During their study of anaemic infants Guest and Brown tested at intervals of approximately three months a considerable number of infants who were being studied closely from birth through their early years. From data thus obtained they attempted to define the normal limits of variability of the red cell count, the total haemoglobin and the haemoglobin content per cell in order to define the borderline of clinically significant anaemia. Their results showed that at one time or another from six months to 2½ years of age the red cells of the majority of healthy infants showed minor alterations of the same pattern as in the development of anaemia. By their method they demonstrated that borderline anaemia occurred much more frequently among seemingly normal infants than is generally appreciated. Moreover, they found that anaemia, when it was recognized in routine clinical work, was usually severe.

In 1936 Mugrage and Andresen made volumetric measurements as well as red cell and haemoglobin estimations on 533 American children, mostly of white parentage, from birth to 13 years. They did not state the birth weights of these infants and only a few were breast-fed. Blood was obtained from the umbilical cord in the newborn, by sinus puncture in the infant, and venipuncture in the older child. Their curve of haemoglobin lay below that of Merritt and Davidson but did not fall as low as Mackay's for normal infants until between 8 and 18 months. At birth their mean haemoglobin value was 17·4 g.; between two and four months 11·4 g.; between four and eight months 12·29 g.; and between 8 and 18 months 11·73 g. % (Table 1). Compared with Merritt and Davidson's figures Mugrage and Andresen's red cell counts were low: at birth 4·88 million cells per c.mm., at two to four months 3·90 million, and thereafter the number slowly increased until at 12 years of age the count reached 4·66 million cells per c.mm. (Table 2 and Fig. 2). For packed cell volume they give the

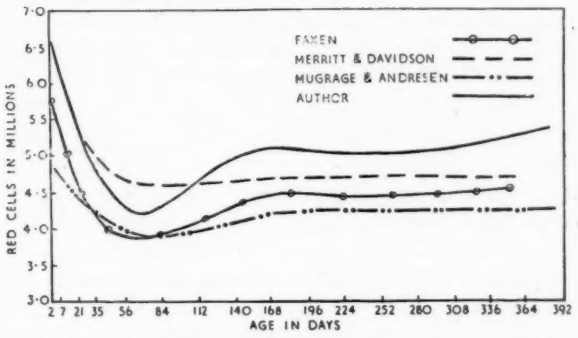

FIG. 2.—Red cell count in infancy according to various authors.

following figures: in cord blood, 53·18%; from two to four months, 34·18%; from four to eight months a value slightly higher and rising after 18 months to 43·8% at 12 years (Table 3 and Fig. 3). They found the mean corpuscular haemoglobin to be 35·1 $\gamma\gamma$ in cord blood, 27·5 $\gamma\gamma$ at 8 to 12 months and equal to adult values at seven years. The mean

TABLE 3

HAEMATOCRIT VALUES IN INFANCY ACCORDING TO VARIOUS AUTHORS

Age	Mugrage and Andresen	Drucker	Present Author
0–48 hours	53·18		62·65
3– 7 days			58·61
8–21 ,,	43·28	54·8	54·04
22–35 ,,		41·8	45·51
6– 8 weeks		37·9	38·95
9–12 ,,	34·18	35·7	34·25
13–16 ,,			34·66
17–20 ,,		37·9	36·27
21–24 ,,	37·37		36·09
25–28 ,,			36·98
29–32 ,,			36·26
33–36 ,,		38·1	35·61
37–40 ,,			36·59
41–44 ,,	36·81		36·35
		38·3	
45–48 ,,			34·87
49–52 ,,			38·00
53–56 ,,			35·00
	36·28 to 18 months	38·8 to 2 years	

corpuscular volume in the cord blood was 108·9 cubic μ, at 12 to 18 months 85·3 cubic μ, and in older children it lay between 89·2 and 93·3 cubic μ, the values for men and women respectively. The mean corpuscular haemoglobin concentration they found to vary little, between 32 and 33·8%.

Before 1937, when Faxen published his work in Sweden, there had been in all investigations some defects in the selection of normal infants. The 374 infants examined from birth to one year of age by Faxen fulfilled all the requirements for normality. Capillary blood was examined and was obtained by pricking the finger tip with an ordinary stilette. Several infants had more than one count made on them during their first year; one had six successive counts, five had five counts and six had four, but the majority had three, two, or only one count made on them. Each of these counts was, from a statistical point of view, regarded as an isolated count and thus Faxen's figures represent the average blood picture of the normal infant community in Sweden. His values for haemoglobin and red cells lie within a very narrow range, but unfortunately his results lack completeness in that he did not measure the volume of packed red cells. After the initial fall of haemoglobin from 23·2 g. % at birth to 12·7 g. at three months a rise to 13·7 g. at five months followed (Table 1 and Fig. 1). These figures were very much higher than Drucker's figures for Danish infants, than Mackay's figures for an artificial normal (i.e. iron-fed) English group, and than Elvehjem's figures for a similar artificial normal group in America. On the other hand they lay close to the findings of Merritt and Davidson on children in New York. Drucker's and Merritt and Davidson's figures showed a fall between the ninth and twelfth months whereas Faxen's figures did not alter. Faxen's red cell count, with an initial value of 5·78 million cells per c.mm., ran parallel to Mugrage and Andresen's but fell below Merritt and Davidson's counts at two to three months and reached a minimum of 3·9 million per c.mm. It then rose until at five months it reached 4·5 million cells per c.mm. and then approximated closely to Merritt and Davidson's counts (Table 2 and Fig. 2). Faxen says that 'the individual variation shows no certain changes in the different ages, but may be somewhat greater in early infancy than at later ages.'

From the above review it will be seen that there have been numerous investigations into the blood picture in infancy but certain deficiencies can be found in each survey, either in the quality of the infants selected or in the completeness of the examinations made. It is only in recent years that the adverse effect of a low birth weight on the blood picture of infants has been recognized and, though all workers agree on the necessity for selecting healthy full-term infants for their survey, Faxen has been the only one to regard a minimum birth weight as one of the essentials of normality. The results of the majority of workers may thus have been affected by the accidental inclusion of infants who, because of a relatively low birth weight or a very rapid gain in weight, may have been suffering from a mild anaemia. Mackay's group of breast-fed infants and infants fed in the later months with iron, together with a similar group of Elvehjem's, constitute artificial normal groups, the development of anaemia presumably having been prevented by the addition of iron to the diet. Even so, Mackay's and Elvehjem's figures for haemoglobin, approximately 86% and 88% in the second six months of life, were much below Faxen's average of 95%. Where red cell counts were made in addition to haemoglobin estimations there is a close approximation between the results of different workers; Merritt and Davidson's figures were high at birth but after the fall at two to three months their findings and those of Faxen and Mugrage and Andresen were almost identical. Volumetric findings were recorded by Drucker and Mugrage and Andresen. All of Drucker's cases were full-term and of 'approximately normal' weight but only one-third were breast-fed. Few of Mugrage and Andresen's cases were breast-fed and the minimum birth weight was not stated. In both of these investigations the grouping of the cases was such that all but gross changes occurring in the blood during the first year of life would probably be overlooked. In spite of this it is noteworthy that, except for a lower initial haematocrit reading in Mugrage and Andresen's cases, subsequent readings lie closely parallel to those of the present series with Drucker's findings at a slightly higher level (Table 3 and Fig. 3).

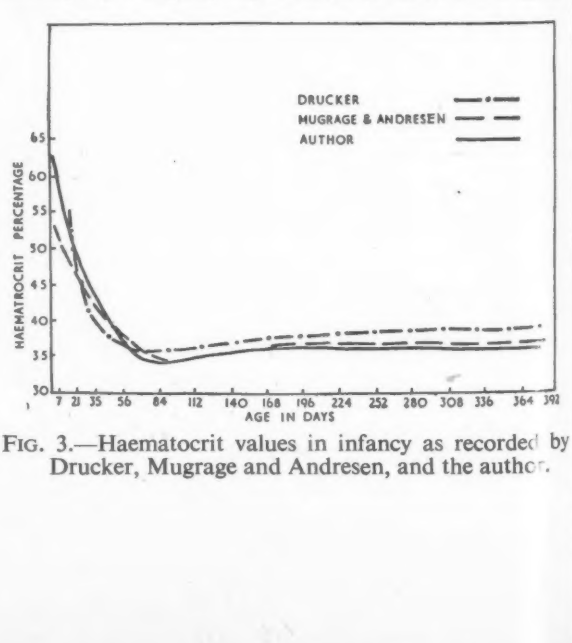

FIG. 3.—Haematocrit values in infancy as recorded by Drucker, Mugrage and Andresen, and the author.

No author shows the individual changes occurring in a sufficient number of normal infants throughout their first year of life to state with authority the limits of the normal blood picture in infancy. With regard to random observations, Faxen's figures may be taken as a criterion of the average in apparently healthy infants. Had he obtained similar results in a control group fed prophylactically with iron it might have been possible to state that his results were not only average but normal for this age.

Material and Method

The infants used in this investigation numbered 249. They were drawn from the population of Birmingham and its suburbs and were mainly the children of artisans with families of one or two. A few came from a poorer working class but most of these babies soon ceased attending. As regards racial differences, the population of this part of England is not a floating one and although there appeared an occasional Scottish or Irish woman amongst the mothers, it is considered that the sample was as purely English as could be obtained. The infants were brought to the clinic at least once a month for blood examinations and 33 continued to attend throughout their first year. Some infants were brought on one or two occasions only. They could not give as valuable information on the changes in the normal blood picture during the first year as did those examined on many occasions but, with the latter, they formed a cross-section of the infant community and from them an average blood picture was obtained.

A clinical examination especially for the purposes of this investigation was not carried out on the mothers as they had all been examined at ante-natal clinics and were delivered at one of the maternity homes of the City of Birmingham Public Health Department. There were no cases of obvious anaemia amongst them although, when seen in the present survey, eight mothers said that they were or had been 'anaemic.' Six had had pyelitis and three albuminuria during pregnancy. A number had received iron during pregnancy.

Twins and infants weighing less than 6 lb. at birth were excluded from the present survey. All but five infants were born within two weeks of the expected date. Of these five, one who was four weeks and two who were three weeks premature were not seen after three weeks of age; another, three weeks premature, was not seen after three months; and the other, although born three weeks before term, weighed 7 lb. 8 oz. at birth and so was regarded as mature and examined at intervals throughout the first year.

Neonatal disease did not appear in the infants selected but the occurrence of pneumonia, pink disease, measles, and other infectious fevers during the later months meant the exclusion of the affected infants after the event. In addition, children who had had more than one attack of bronchitis were excluded. As the majority of the infants had one or two minor illnesses in their first year, those who had not ceased to gain weight were regarded as normal. In this way were included a number of infants who had had more than one cold, three who had had one attack of bronchitis, and five who had had mild gastro-enteritis.

Infants were excluded if at any time their weight fell more than 10% below the average for their age and birth weight. One breast-fed infant and seven artificially fed infants weighed at one year over 10% more than their expected weight, but these were not excluded from the series representing a cross-section of the community; the breast-fed infant was excluded from the breast-fed normal series when its weight became excessive.

Most of the infants were breast-fed for the first three months. After that time most of them were artificially fed while some were partly breast-fed and partly artificially fed. In all cases orange juice and cod liver oil or their equivalents were started at about two months of age. Additions to milk feeds were begun at five or six months and were increased until at nine months the infant was fully weaned and was taking approximately one and a half pints of cows' milk daily with cereals, fruit, vegetables, egg, fish, and small amounts of liver. The quantity and variety of foods were increased during the next three months so that at one year of age the infant was on a well-balanced mixed diet. Prophylactic doses of iron were given to certain infants in an attempt to protect them from nutritional anaemia and so create an 'ideal normal' series. A number of mothers succeeded in giving their infants sufficient iron for not less than three months. The findings in these infants were compared at 12 months with those in babies who were not given iron at all during their first year.

No special attention was paid to the time of day at which the samples of blood were taken, although the majority were collected in the morning. Usually a particular child was seen always at the same time of day so that the counts of each individual were presumably comparable throughout. It is noteworthy, however, that Drucker (1923) did not find that the time of day or the relation to meals affected the results in any way.

The following routine was used for collecting blood from the infants. The baby's heel was warmed in a bowl of warm water, dried, cleaned with ether, and pricked by means of a sharp spring-lancet. This produced a free flow of blood which was collected into a small tube of total capacity 0·25 ml. containing two or three particles of dry heparin and a small piece of shot. About 0·1 ml. of blood was obtained and thoroughly mixed with the heparin and the tube was corked with a rubber bung. The use of heparin in tubes allowed ease of transport and the duplication of estimations on the one sample.

Haemoglobin, red cell, and haematocrit estimations were carried out on each sample. The haemoglobin was estimated by the method of Haldane, and eight Haldane pipettes and diluting tubes were used throughout the investigation. Heparinized blood was drawn up to the 0·02 ml. mark on a Haldane pipette and washed into distilled water in a diluting tube. Coal gas was then blown over the surface of the haemolysed blood for two minutes, and the blood diluted with distilled water to match the standard. Haemoglobin dilutions were matched against artificial daylight and the result was

expressed as a percentage, 100% being equivalent to 13·8 g. of haemoglobin per 100 ml. of blood. For the red cell count six standard red cell pipettes and one Hawksley's 'improved Neubauer' counting chamber were used over the whole period. Heparinized blood was drawn up to the 0·5 mark, and then Hayem's diluting fluid up to the 101 mark. The cells in 80 squares, each of 1/400 sq. mm. area, were counted on each side of the counting chamber and the average taken. Calculation then gave the average red cell count per ml. of blood. In the latter part of the investigation duplicate red cell counts were made on the same sample of blood and the average taken. For packing the red cells a special high-speed centrifuge made by Baird and Tatlock, with tubes graduated from 0 to 100 with an internal diameter of 1 mm., was used. The tubes were 5 cm. long, of thick glass, and were open at both ends; they were inserted into accurately fitting brass containers with rubber stoppers at each end and with a screw cap to ensure that the close fit of tube against rubber was maintained. The tubes were centrifuged at 8,000 revolutions per minute until packing was complete. Results were expressed as the percentage of packed red cells per unit volume of blood.

In an investigation such as the present the potential sources of error are many. It has been stated by various authors that capillary blood obtained from different parts of the body at the same time, for instance from the heel and the lobe of the ear, may show considerable variations, but Drucker (1923) considers that this is due to faulty methods of obtaining blood. It has also been stated that blood from one part of the body may vary widely at different times, but Drucker did not confirm this in children over one month of age. In the present investigation the heel was used instead of the ear because of its convenience and because physical conditions could be kept constant more easily. Throughout the survey care was taken to ensure continual sharpness of the lancet as Drucker showed that bluntness leads to greater variations and higher values. As dilutions were not made at the time of collection of the blood, dry heparin, which does not affect the osmotic equilibrium of cells and plasma, was used as an anticoagulant. Throughout the investigation dilutions were usually made within two or three hours of collection, but in a few cases the heparinized blood was left in the corked tubes overnight. Comparative counts showed that such a delay did not introduce any recognizable error.

It was realized that errors in estimating haemoglobin might arise from variations in the Haldane pipettes, in the diluting tubes, or in the standard haemoglobin tube; in counting the red cells they might arise from variations in the red cell pipettes or from the counting chamber; and, in measuring the volume of packed cells, from variations in the haematocrit tubes.

All glassware used in this investigation was supplied by Messrs. Hawkesley and Sons, Ltd., and was used with their guarantee of accuracy. The one haemoglobin standard was guaranteed accurate at the beginning of the investigation and was tested again at the end of the investigation and found still to be accurate.

Manipulative technique was standardized and kept unaltered so that the personal error might remain at a minimum. As the technical work was never delegated the personal error is presumed to have remained the same throughout and to have affected the results equally. In repeated estimations on the same sample of blood it was found that the range of error in reading haemoglobin and haematocrit values and in counting red cells was in each case ±2%. Such an error, of significance in a solitary estimation, may be presumed to operate equally about the mean where a sufficient number of estimations are made on a group of infants or when a statistical analysis is made of a smaller number of such estimations.

Results of the Present Investigation

The present work may be divided into two main sections. This paper is the first section and deals with an analysis of approximately 1,200 blood counts made on 249 infants, and with the establishment of mean values for the haemoglobin, red cell count, and haematocrit at ages ranging from birth to 13 months.

The 249 infants, alike in all other respects, differed from one another in one important particular, that of feeding. According to the method of feeding the infants were placed in one of four groups. The first group consisted of all the infants in the survey whether they were breast-fed, artificially fed, fed on a mixture of breast milk and cows' milk or given iron as a prophylactic measure. This group formed a cross-section of the healthy infant population. The second group consisted of all cases who were breast-fed from birth to at least six months of age. This group was regarded as the true normal of the infant population. The third group consisted of all infants who were artificially fed from birth: in addition, any infants who had been completely weaned before the age of three months (90 days) were added to this group after they reached the age of six months. Readings in this group were compared and contrasted with those of the breast-fed group. The fourth group consisted of a small number of infants of approximately 12 months of age who had been given adequate prophylactic doses of iron for at least three months. This last group formed an 'ideal normal' for one year of age and was used as a criterion of the normality of the breast-fed and artificially fed groups of the same age.

In the first three feeding groups, the blood counts were arranged in age-groups from birth to 13 months. The grouping was 0 to 48 hours, 3 to 7 days, 8 to 21 days, 22 to 35 days, 36 to 56 days, and thereafter consisted of periods of four weeks. The mean values and their standard errors for haemoglobin, red cell count, and haematocrit were calculated from the readings obtained in each age-group within each feeding group and alterations in these values during the first year of life were observed. From these absolute values were calculated the mean corpuscular haemoglobin, the mean corpuscular volume, and the mean corpuscular haemoglobin concentration. The colour index was calculated from the red cell count and the haemoglobin value expressed as a percentage where 100% corresponded to 13·8 g. of haemoglobin per 100 ml. of blood. The values so obtained in the group of breast-fed infants have been

taken as an arbitrary standard and with them have been compared the results from other methods of feeding and the findings of other workers.

Haemoglobin. Table 4 shows the mean values, with their standard errors, of the haemoglobin of the group of breast-fed infants from birth to 13 months of age. The means are expressed as g. per 100 ml. blood and as the equivalent percentage Haldane. The number of cases in each age-group decreased rapidly after the first three weeks so that from the seventeenth week onwards the number was less than ten. In the statistical analysis of these figures corrections were made for the use of such small numbers. At birth the haemoglobin level was high, 20·5 g. per 100 ml. blood or 148·6% Haldane: it then fell rapidly and steadily to a minimum of 11·8 g. or 86% at two to three months of age: thereafter it rose slightly to a second lower maximum of 12·6 g. or 91% at four to five months and then fell slightly again to an average of 11·7 g. or 85% (range 11·3 to 12·4 g. or 82% to 90%).

TABLE 4

HAEMOGLOBIN VALUES IN BREAST-FED INFANTS

Age	Number of Cases	Haemoglobin		
		Percentage Haldane (100% = 13·8 g.)		G. per 100 ml. blood
		Mean	Standard Error	
0–48 hours	87	148·66	1·29	20·5
3– 7 days	100	141·32	1·20	19·4
8–21 ,,	96	130·77	1·22	18·0
22–35 ,,	33	110·03	2·09	15·2
6– 8 weeks	27	96·11	2·31	13·3
9–12 ,,	32	86·00	2·12	11·8
13–16 ,,	24	87·38	2·45	12·0
17–20 ,,	14	91·14	3·21	12·6
21–24 ,,	9	89·78	4·00	12·4
25–28 ,,	11	90·00	3·62	12·4
29–32 ,,	10	88·40	3·62	12·2
33–36 ,,	8	86·00	4·00	11·8
37–40 ,,	8	86·13	4·00	11·8
41–44 ,,	5	85·20	4·90	11·7
45–48 ,,	6	82·17	4·54	11·3
49–52 ,,	5	90·80	5·37	12·5
53–56 ,,	4	84·50	6·00	11·7

These values agree, after the age of six months, with those of Mackay and the majority of other workers, but lie at a lower level than those of Williamson, Merritt and Davidson, and Faxen (Fig. 1 and Table 1).

A statistical examination of the results showed that the falling values of haemoglobin in the age-groups from birth to two to three months were highly significant but that the subsequent rise as shown in Table 4 and Fig. 1 was not significant.

Table 5 shows the mean values, with their standard errors, of the haemoglobin of the group of artificially-fed infants from birth to 13 months of age. The age-groups up to 12 weeks contained 10 cases or less, from 13 to 40 weeks between 20 and 32 cases and from 41 to 56 weeks approximately 10 cases. Fig. 4 is a graphical representation of these results compared with those of the breast-fed group. Comparison of Tables 4 and 5 and an examination of Fig. 4 show that the haemoglobin values for breast-fed and artificially fed infants are extremely close, that their curves are virtually parallel, and that the artificially fed group lies at the lower level.

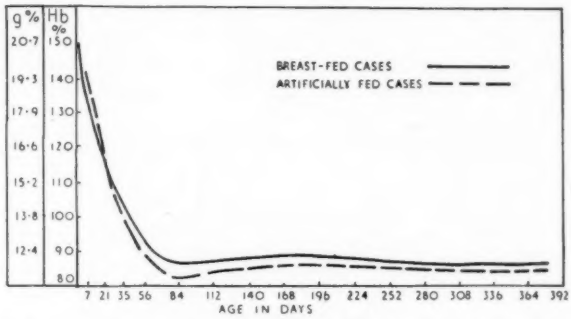

FIG. 4.—Percentage haemoglobin in breast-fed and artificially fed cases.

Table 6 shows the mean values, with their standard errors, of the haemoglobin from birth to 13 months of all infants, whatever the type of feeding. Fig. 5 depicts these findings compared with those of breast-fed infants. The numbers in each age-group were much greater than in the breast-fed and artificially fed groups: up to three weeks of age the groups contained between 129 and 141 cases, from 3 to 40 weeks between 40 and 72 cases, and from 41 to 56 weeks between 19 and 28 cases.

TABLE 5

HAEMOGLOBIN VALUES IN ARTIFICIALLY FED INFANTS

Age	Number of Cases	Haemoglobin	
		Percentage Haldane (100% = 13·8 g.)	
		Mean	Standard Error
0–48 hours	9	146·11	4·00
3– 7 days	8	147·88	4·24
8–21 ,,	10	135·40	3·79
22–35 ,,	4	113·50	6·00
6– 8 weeks	5	94·60	5·37
9–12 ,,	6	81·33	4·90
13–16 ,,	32	86·88	2·12
17–20 ,,	31	88·45	2·12
21–24 ,,	29	89·86	2·23
25–28 ,,	28	87·75	2·27
29–32 ,,	28	85·57	2·27
33–36 ,,	24	84·83	2·45
37–40 ,,	20	87·00	2·68
41–44 ,,	14	84·14	3·21
45–48 ,,	13	83·53	3·33
49–52 ,,	9	87·56	4·00
53–56 ,,	11	81·64	3·62

TABLE 6

HAEMOGLOBIN VALUES IN ALL CASES

Age	Number of Cases	Haemoglobin	
		Percentage Haldane (100% = 13·8 g.)	
		Mean	Standard Error
0–48 hours	129	149·60	1·06
3– 7 days	141	143·81	1·01
8–21 ,,	134	131·72	1·03
22–35 ,,	56	110·50	1·60
6– 8 weeks	51	95·16	1·68
9–12 ,,	72	85·49	1·41
13–16 ,,	65	87·42	1·49
17–20 ,,	56	89·23	1·59
21–24 ,,	53	89·72	1·65
25–28 ,,	49	88·67	1·71
29–32 ,,	57	86·37	1·57
33–36 ,,	45	85·62	1·77
37–40 ,,	40	86·50	1·90
41–44 ,,	28	84·96	2·27
45–48 ,,	27	83·41	2·31
49–52 ,,	20	86·90	2·68
53–56 ,,	19	82·32	2·75

Comparison of Tables 6 and 4 and an examination of Fig. 5 show that the same remarks apply to this group of infants, a cross-section of the healthy infant population, as to the artificially fed group, i.e. that its haemoglobin values lie extremely close to but at a lower level than those of the breast-fed group.

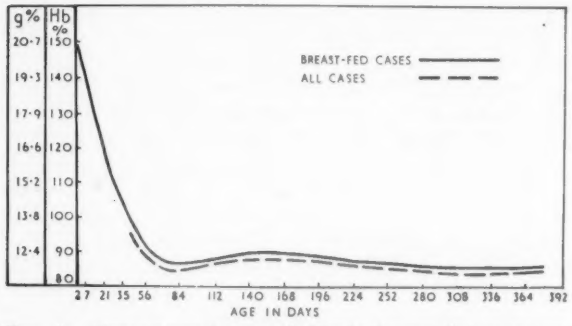

FIG. 5.—Percentage haemoglobin in breast-fed cases and all cases.

Comparison of Figs. 4 and 5 show that the mean haemoglobin values in ' all cases ' lie between those of the artificially fed group and those of the breast-fed group. This observation is supported by statistical analysis in which it was shown that there was a characteristic range of values associated with each age whatever the method of feeding but the actual value within this range was dependent upon the method of feeding. At any particular age the differences between the various methods of feeding were too small to be statistically significant but they were consistent enough to be highly significant when the mean was taken for each method over the whole range of age-groups. This was demonstrated graphically by the parallelism of the curves in the three methods of feeding. In other words, in a group of healthy infants the method of feeding produces small but significant effects on the haemoglobin level. Artificially fed infants have the lowest average haemoglobin values. Slightly higher values are found in partly breast-fed infants and slightly higher values still are found in fully breast-fed infants. The values in the artificially fed group were well within the accepted lower limits of normal and at no time did this group come under the suspicion of anaemia.

At approximately 12 months of age the haemoglobin values of a small group of infants who had been given adequate prophylactic doses of iron for at least three months were compared with those of a group of breast-fed infants and also with those of a group of artificially fed infants of the same age. Table 7, showing the me.. haemoglobin values with their standard errors, ma..s this comparison clear and includes also the values for the red cell count and the haematocrit. The one statistically significant difference in these blood findings is in the haemoglobin means of artificially fed and iron-fed infants. The difference between these means is 10·5 which has a standard error of 3·68 so that the odds against this difference being due to chance lie between 100 and 1,000 to 1. No other difference is significant, either for the red blood corpuscles, the haematocrit or the remaining haemoglobin means, but there is some indication that increasing iron intake influences all three characteristics as the three sets of means are consistent in showing slight increases in the order artificially fed, breast-fed, iron-fed.

TABLE 7

BLOOD FINDINGS AT APPROXIMATELY 12 MONTHS OF AGE

Method of Feeding	Number of Cases	Haemoglobin		Red Blood Corpuscles		Haematocrit	
		Mean	Standard Error	Mean	Standard Error	Mean	Standard Error
Artificially Fed	13	82·9	2·43	5·14	0·11	36·12	0·80
Breast-Fed	10	87·3	2·77	5·21	0·12	36·75	0·91
Iron-Fed	10	93·4	2·77	5·45	0·12	38·95	0·91

In Table 1 are shown the haemoglobin values (expressed as percentages) during the first year of life as recorded by various authors. It may be seen that the high level at birth and the subsequent fall in haemoglobin values are common to all workers whereas the slight rise and slighter second fall as seen in the present series are not shown by all. Individual variations in the general pattern are great: for instance, at birth the lowest value for haemoglobin is 125% (Mugrage and Andresen), the highest 160% to 170% (Williamson, Appleton, Elvehjem, Merritt and Davidson, and Faxen), with the values of Mackay and the present author lying midway between these extremes at approximately 145%. (Drucker's figure of 123% for his earliest age-group at two to three weeks of age cannot justly be compared with results in infants a few hours to a few days old.) There appears to be no convincing explanation of this great variation in the haemoglobin values at birth. Mugrage and Andresen's low value may possibly be explained by the fact that the blood was obtained from the umbilical cord at birth before the flow had stopped; all other workers obtained blood from the capillary circulation of the infant, and in some cases stasis in the capillaries may have led to an abnormally high count being recorded. The 20% difference between the figures for English children at birth and those of American and Swedish children still remains unexplained. It is possible that racial differences may account for the disparity or the time at which the umbilical cord is tied. For the remainder of the first year of life the fluctuations of the haemoglobin level as found by different workers may follow one of three types of curve (Fig. 1). In the first type there is a steady fall throughout the first year to the lowest level at 12 months of age (Williamson and Appleton); in the second type an initial fall to two or three months of age is followed by a slight rise which is maintained to 12 months of age (Mackay, Faxen, Elvehjem's iron-fed group): in the third type the fall and rise is followed by a second slight fall (Drucker, Elvehjem's untreated group, Merritt and Davidson, Mugrage and Andresen, the present author).

In trying to account for the above differences an explanation of the first type of curve may be found in the method of grouping followed by Williamson and Appleton. Both these authors grouped cases aged from two weeks to two months in one group and those aged from three months to five months in the next group. Any finer changes occurring at, say, four-weekly intervals would be lost in such a grouping and any minimum occurring, say, at two to three months of age would be offset by higher values at earlier and later ages. Mugrage and Andresen, who grouped cases aged from two to four months together, found the average haemoglobin values for the first year of life at their lowest at this age. In the present series of cases where serial counts were made on individual infants at four-weekly intervals the minimum was found to occur from six weeks to four months of age. Any curve, therefore, constructed from the mean of a number of individuals may not reflect the extent of this primary fall, the minimum being offset by higher values occurring in other cases at the same age. The second and third types of curve are alike in showing a primary fall followed by a rise. In the second group, comprising Mackay's and Faxen's groups and Elvehjem's group of infants treated with iron, this rise is maintained throughout the remainder of the year. In Mackay's series a second fall is probably prevented by the fact that the infants chosen to constitute the normal were given prophylactic doses of iron from the third month onwards, so that the development of an undetected anaemia in an apparently healthy group of children was presumably prevented. Elvehjem's group of treated

TABLE 8

RED BLOOD CORPUSCLES (MILLIONS PER C.MM.) IN INFANCY

Age	Breast-Fed Infants			Artificially Fed Infants			All Cases		
	No. of Cases	Mean	Standard Error	No. of Cases	Mean	Standard Error	No. of Cases	Mean	Standard Error
0–48 hours	87	6·54	0·06	9	6·40	0·20	129	6·60	0·05
3– 7 days	100	6·30	0·06	8	6·66	0·21	141	6·39	0·05
8–21 ,,	96	5·85	0·06	10	6·05	0·19	134	5·85	0·05
22–35 ,,	33	5·02	0·10	4	5·19	0·30	56	5·02	0·08
6– 8 weeks	27	4·53	0·11	5	4·45	0·26	51	4·47	0·08
9–12 ,,	32	4·14	0·10	6	3·92	0·24	72	4·14	0·07
13–16 ,,	24	4·42	0·12	32	4·66	0·10	65	4·56	0·07
17–20 ,,	14	4·91	0·16	31	4·94	0·10	56	4·93	0·08
21–24 ,,	9	5·03	0·20	29	5·19	0·11	53	5·12	0·08
25–28 ,,	11	5·14	0·18	28	5·18	0·11	49	5·19	0·08
29–32 ,,	10	5·07	0·18	28	5·18	0·11	57	5·11	0·08
33–36 ,,	8	4·72	0·20	24	5·28	0·12	45	5·12	0·09
37–40 ,,	8	5·23	0·20	20	5·49	0·13	40	5·29	0·09
41–44 ,,	5	5·17	0·24	14	5·28	0·16	28	5·20	0·11
45–48 ,,	6	4·96	0·22	13	5·26	0·16	27	5·14	0·11
49–52 ,,	5	5·33	0·26	9	5·38	0·20	20	5·33	0·13
53–56 ,,	4	5·41	0·30	11	5·36	0·18	19	5·30	0·14

infants was probably protected in a similar manner. Faxen's group of infants was not protected in this way but his selection of healthy infants was more strict, particular stress being laid on a minimum birth weight of 3,000 g., on breast-feeding, on freedom from sickness during the first year of life, and on the early addition of iron-containing foods to a milk diet. Even so he found that the diameter of the red cells in healthy children in the second half-year of life showed 'a slight change in the direction of hypochromatic anaemia' and 'the relatively low percentage of haemoglobin per blood corpuscle in the second half-year is associated with the marked predisposition to hypochromatic anaemias occurring at this age.'

The third group, characterized by a fall of haemoglobin in the second half-year of life, comprises the results of Drucker, Elvehjem, Merritt and Davidson, Mugrage and Andresen and the present author. The inclusion of some infants of low birth weight may possibly account for the second fall in the haemoglobin level observed by most of these authors as such infants often make a rapid gain in weight, and Mackay found that 'from six to twelve months old the haemoglobin level was correlated with the rate of growth: babies who made the largest percentage increase in weight over their birth weight tend to have the lowest haemoglobin levels.' All these investigators were careful to select full-term, healthy infants for their series and the present author made a minimum birth weight (6 lb.) an additional criterion of normality. (In Faxen's cases the minimum birth weight was 3,000 g. or 6 lb. 9 oz.) In the breast-fed group in the present series infants who at the age of one year had made an excessive gain in weight (i.e. more than three times their birth weight plus 10%) were excluded. Even so it was found in serial blood counts in apparently healthy infants that the evidences of the onset of nutritional anaemia could be found before the fact became apparent clinically and before an isolated blood count could properly be said to indicate anaemia. It is probable therefore that, with the exception of Mackay's and Elvehjem's ideal normal groups, the results of all workers are affected in this way by the unsuspected inclusion of mildly anaemic infants and that such is the explanation of a fall in the mean haemoglobin level in some cases in the second half-year of life.

The difference between the actual haemoglobin value found by different authors in the second six months of life still requires an explanation. Williamson, Merritt and Davidson, and Faxen give values never less than 90% (Faxen's cases show an average of 95%) whereas all other authors show an average of approximately 85% over the same period. Mugrage and Andresen examined venous blood whereas all other authors examined capillary blood. As some of the earliest and latest work on the haemoglobin appears in each of these categories, any refinements in technique or stricter standards of normality used in later work will not account for such differences. In the present series of cases, though results in individual age-groups varied from 82% to 90%, the average for the second half-year was 85%, and in Mackay's cases the giving of iron did not raise the haemoglobin level above 86% in the second half-year of life. Both these results were obtained in English children, the former in Birmingham and the latter in London. From this it appears that, anaemia excluded, the wide variation in haemoglobin values recorded by workers in different countries (in America by workers in different parts of the country) is probably due to differences in race.

Red Blood Corpuscles. Table 8 shows the mean values, with their standard errors, of the red cell count in breast-fed infants of the present series from birth to 13 months of age. These values are represented graphically in Fig. 6. In each age-group the number of

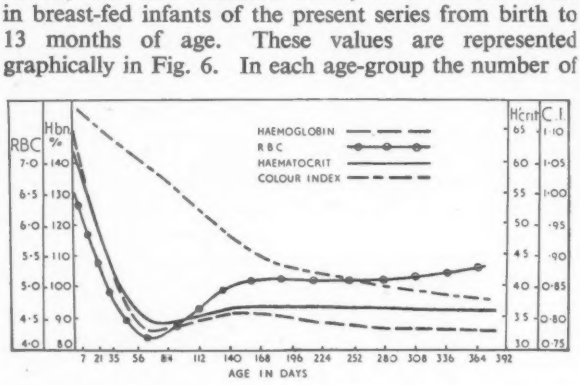

FIG. 6.—Changes in haemoglobin, red cell count, haematocrit, and colour index in breast-fed infants during the first year of life.

cases was the same as for the haemoglobin. It may be seen that the changes in the red cell count followed a course somewhat similar to that of the haemoglobin, that is, a high level at birth was followed by a steady fall to a minimum at about three months of age; thereafter there was a rise to a second but much lower maximum at about seven to eight months and this second level was maintained throughout the remainder of the year. At birth the mean red cell count was 6·54 millions per c.mm.; at 9 to 12 weeks it was 4·14 millions; at 25 to 28 weeks 5·14 millions and thereafter varied from 4·72 millions at 33 to 36 weeks to 5·41 millions at 53 to 56 weeks.

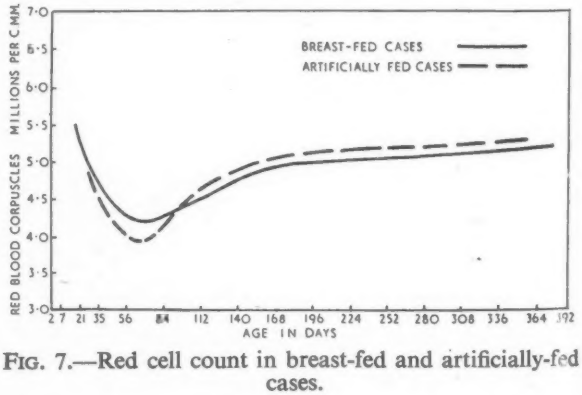

FIG. 7.—Red cell count in breast-fed and artificially-fed cases.

A statistical analysis of these figures establishes the reality of the fall in the red cell count from birth to approximately three months of age and also of the subsequent rise to a fairly stable level in the second half-year of life. That is to say, the changes shown in the present series

of cases are not due to a chance selection of unusual infants but truly represent the mean red cell count in this particular infant population from birth to 13 months of age.

In Table 8 also are set out the mean red cell counts with their standard errors of artificially fed infants and 'all cases' in the present series.

In Fig. 7 a comparison is made of the red cell counts in breast-fed and artificially fed infants and in Fig. 6 of breast-fed cases and 'all cases.' It may be seen that the curves are extremely close but the initial fall in the red cell count is greatest in the artificially fed, least in the breast-fed, and with the curve for 'all cases' lying between the other two. After the age of four months the positions are reversed, the highest curve being that of artificially fed cases, the lowest of breast-fed cases, with the curve of 'all cases' again lying between the other two. In spite of the parallelism of these curves from the fourth month onwards statistical analysis does not distinguish any difference between the red cell counts of the three feeding groups.

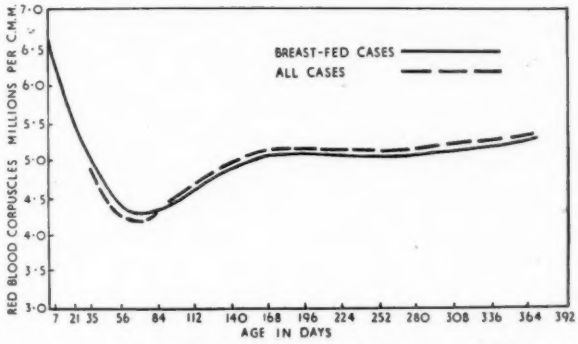

FIG. 8.—Red cell count in breast-fed cases and all cases.

TABLE 9

ABSOLUTE VALUES OF RED CELL CHARACTERISTICS IN BREAST-FED INFANTS FROM BIRTH TO 13 MONTHS

Age	Haemoglobin (G. per 100 ml. blood)	Haemoglobin (Percentage Haldane)	Red Blood cells (m. per c.mm.)	Haematocrit (%)	Mean Corpuscular Haemoglobin (γγ)	Mean Corpuscular Volume (c.μ.)	Mean Corpuscular Haemoglobin Concentration (%)	Colour Index
0–48 hours	20·5	148·6	6·54	62·65	31·3	95·8	32·7	1·13
3– 7 days	19·4	141·3	6·30	58·61	30·8	93·0	33·1	1·12
8–21 ,,	18·0	130·7	5·85	54·04	30·7	92·3	33·3	1·12
22–35 ,,	15·2	110·0	5·02	45·51	30·2	90·6	33·4	1·10
6– 8 weeks	13·3	96·1	4·53	38·95	29·3	85·9	34·1	1·05
9–12 ,,	11·8	86·0	4·14	34·25	28·5	82·7	34·4	1·04
13–16 ,,	12·0	87·4	4·42	34·66	27·1	78·4	34·6	0·99
17–20 ,,	12·6	91·1	4·91	36·27	25·6	73·8	34·7	0·93
21–24 ,,	12·4	89·8	5·03	36·09	24·6	71·7	34·3	0·89
25–28 ,,	12·4	90·0	5·14	36·98	24·1	71·9	33·5	0·87
29–32 ,,	12·2	88·4	5·07	36·26	24·0	71·5	33·6	0·87
33–36 ,,	11·8	86·0	4·72	35·61	25·0	75·4	33·1	0·91
37–40 ,,	11·8	86·1	5·23	36·59	22·5	69·9	32·2	0·82
41–44 ,,	11·7	85·2	5·17	36·35	22·6	70·3	32·1	0·83
45–48 ,,	11·3	82·2	4·96	34·87	22·7	70·3	32·4	0·83
49–52 ,,	12·5	90·8	5·33	38·00	23·4	71·3	32·9	0·85
53–56 ,,	11·7	84·5	5·41	35·00	21·6	64·6	33·4	0·79

A graphical comparison of the red cell count with the haemoglobin is seen in Fig. 6. The curves of these two characteristics lie roughly parallel until about 10 weeks of age; the curve of the red cell count then rises rapidly until a second steady level is reached at about six months of age; at about 12 months of age the curve again rises slightly. The haemoglobin curve shows a slight rise at about the fifth month followed by a slight fall to a level maintained throughout the remainder of the year. This change in the relationship of the red cells and the haemoglobin is most clearly expressed by the colour index and the mean corpuscular haemoglobin which show a rapid fall from birth to about six months of age followed by a much slower decline (Table 9, Figs. 6 and 9). It is an indication of the change in the red cells

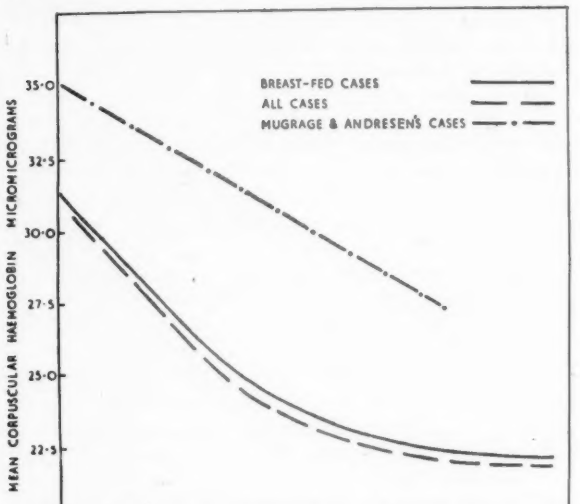

FIG. 9.—Mean corpuscular haemoglobin in breast-fed cases, all cases, and Mugrage and Andresen's cases.

from a hyperchromic state in the newly-born to a state of hypochromia in the year-old baby.

Table 2 shows the red cell counts recorded by various authors. Four workers have counted the red blood cells in infancy, few compared with the number who measured the haemoglobin, but, as with the haemoglobin, the same type of course is seen: an initial high level, a rapid fall to a low level, followed by a slow rise to a second steady maximum. The actual values recorded by the different authors vary considerably. Table 2 and Fig. 2, its graphical counterpart, make this clear. In Fig. 2, two types of curve are seen. One, in which the fall and rise are well defined, is seen in the work of Faxen and that of the present author and the other, in which the curve is much flatter, in that of Merritt and Davidson and Mugrage and Andresen. At birth Mugrage and Andresen's figure, like that for their haemoglobin, is low, 4·86 million cells per c.mm.; Merritt and Davidson's and Faxen's are much higher, 5·95 and 5·78 millions respectively, and the present author's is still higher, 6·54 million cells per c.mm. Except for Merritt and Davidson's value of 4·61 million cells at four to five months, all authors show lowest values of approximately 4 million cells at two to three months of age. (Mugrage and Andresen's and Faxen's lowest counts were 3·9 million, the present author's 4·14 million). All four workers find that at about the fifth month a fairly stable value is reached, the highest value at this age, 5 million cells per c.mm., being recorded by the present author, the next, 4·7 million, by Merritt and Davidson, the third, 4·45 million, by Faxen, and the lowest value at this age, approximately 4·23 million cells per c.mm. by Mugrage and Andresen.

Examination of Fig. 2 shows that the curves of Merritt and Davidson's figures and those of Mugrage and Andresen, though roughly parallel, are widely separated. Their separation represents a difference of approximately 500,000 cells per c.mm., Merritt and Davidson's figures being the higher. American children were examined in both cases, but whereas Merritt and Davidson used capillary blood from children of mixed racial origin, Mugrage and Andresen used venous blood mostly from children of white parents. It is unlikely that the personal element could account for the difference of approximately half a million cells at each age-group and, except possibly at birth, it is also unlikely that such differences are due to the use of capillary blood on the one hand and venous blood on the other. One possible explanation is that early cases of anaemia have unwittingly been included in some of the groups. As an increase in the red cell count is the earliest expression of anaemia it is possible that the group with the highest red cell counts contains a disproportionate number of such cases. A second explanation is that such differences are racial, Mugrage and Andresen having examined children of white parents and Merritt and Davidson children of mixed race.

Fig. 2 shows that the curve of Faxen's cases lies parallel to that in the present series but at a much lower level, representing a difference of at least half a million cells per c.mm. from the fourth month onwards. Personal differences in technique could not account for such a great difference in the red cell counts in these two series. It is possible that in the present series, where the minimum birth weight was 9 oz. less than Faxen's minimum, the higher red cell count was due to the inclusion of a disproportionate number of unsuspected early cases of anaemia. Racial differences may also have been a contributing cause.

No satisfactory explanation can be advanced for the differences in the two types of curve, flat after the initial fall in the case of Merritt and Davidson and Mugrage and Andresen, and with a greater fall and rise in the case of Faxen and the present author.

After the age of four months the highest red cell counts were found in the present series of English infants, the second highest in Merritt and Davidson's series of American children of white parentage, the next in Faxen's series of Swedish children, and the lowest in Mugrage and Andresen's series of American children of mixed race.

Haematocrit. Table 10 shows the mean values, with their standard errors, of the packed cell volume in the present series of breast-fed infants at ages ranging from birth to 13 months. For the first three weeks the number

of cases in each age-group was at least 70; from three weeks onward the number was less than 20, and from five months onwards less than 10. In the statistical analysis of these results corrections were made for the use of such small numbers. The results are expressed as a percentage and the findings follow approximately the same course as the haemoglobin and the red cell count, that is to say, an initial high value is followed by a fall and this fall is followed by a slight rise to a level that remains practically unaltered for the rest of the year. At birth the packed cell volume was 62·65%, at two to three months 34·25% and thereafter rose slightly and remained at an average of 36% for the rest of the year. Analysis showed that there was a statistical difference between the results in succeeding age groups from birth to 9 to 12 weeks of age whereas from that time onwards any differences were too slight to be significant.

TABLE 10
HAEMATOCRIT VALUES IN BREAST-FED INFANTS

Age	Number of Cases	Haematocrit	
		Mean (%)	Standard Error
0–48 hours	70	62·65	0·57
3– 7 days	79	58·61	0·53
8–21 ,,	72	54·04	0·54
22–35 ,,	16	45·51	0·93
6– 8 weeks	11	38·95	1·02
9–12 ,,	15	34·25	0·94
13–16 ,,	14	34·66	1·08
17–20 ,,	11	36·27	1·42
21–24 ,,	8	36·09	1·77
25–28 ,,	9	36·98	1·60
29–32 ,,	10	36·26	1·60
33–36 ,,	8	35·61	1·77
37–40 ,,	9	36·59	1·77
41–44 ,,	5	36·35	2·17
45–48 ,,	7	34·87	2·01
49–52 ,,	5	38·00	2·38
53–56 ,,	4	35·00	2·66

In Table 11 are set out the mean haematocrit values, with their standard errors, of breast-fed infants, artificially fed infants, and ' all cases ' in the present series from birth to 13 months. The number of cases in the artificially fed group was less than 10 in the first three months, between 20 and 26 from three to ten months, and thereafter was approximately 11. The numbers were much greater in the group of ' all cases ' averaging 100 in the first three weeks, never falling below 40 from the third to the tenth month and thereafter ranging from 19 to 26 in each age-group. Fig. 10, showing the haematocrit values in breast-fed and artificially fed infants, is a graphical representation of Table 11 with the curve for

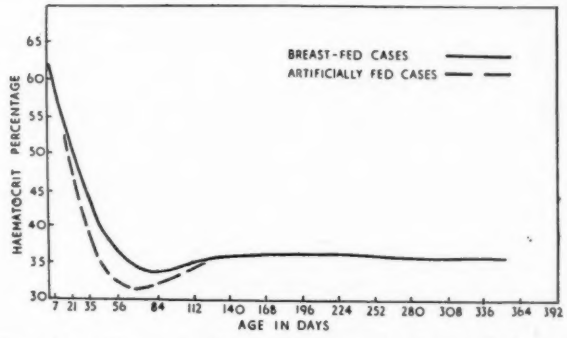

FIG. 10.—Haematocrit percentage in breast-fed and artificially-fed cases.

TABLE 11
HAEMATOCRIT VALUES IN INFANCY (VOLUME OF PACKED RED CELLS PER CENT.)

Age	Breast-Fed Infants			Artificially Fed Infants			All Cases		
	No. of Cases	Mean (%)	Standard Error	No. of Cases	Mean (%)	Standard Error	No. of Cases	Mean (%)	Standard Error
0–48 hours	70	62·65	0·57	7	63·71	1·77	98	63·25	0·47
3– 7 days	79	58·61	0·53	6	61·03	1·88	103	59·76	0·45
8–21 ,,	72	54·04	0·54	8	55·56	1·68	100	54·51	0·46
22–35 ,,	16	45·51	0·93	3	47·83	2·66	30	44·26	0·71
6– 8 weeks	11	38·95	1·02	2	33·75	2·38	22	36·95	0·74
9–12 ,,	15	34·25	0·94	3	31·43	2·17	39	33·90	0·63
13–16 ,,	14	34·66	1·08	21	34·91	0·94	40	35·04	0·66
17–20 ,,	11	36·27	1·42	22	35·56	0·94	43	36·00	0·70
21–24 ,,	8	36·09	1·77	26	36·87	0·99	48	36·79	0·73
25–28 ,,	9	36·98	1·60	22	35·64	1·00	41	36·51	0·76
29–32 ,,	10	36·26	1·60	26	36·02	1·00	58	36·32	0·70
33–36 ,,	8	35·61	1·77	23	36·41	1·08	43	36·35	0·78
37–40 ,,	9	36·59	1·77	20	36·77	1·19	41	36·72	0·84
41–44 ,,	5	36·35	2·17	13	36·12	1·42	26	36·43	1·00
45–48 ,,	7	34·87	2·01	13	35·79	1·47	27	35·48	1·02
49–52 ,,	5	38·00	2·38	9	36·62	1·77	19	36·83	1·19
53–56 ,,	4	35·00	2·66	11	36·06	1·60	19	35·58	1·22

'all infants' omitted for the sake of clarity. From approximately three weeks to four months there is a slight divergence of the curves but thereafter they are indistinguishable. The curve for 'all infants' lies between the artificially fed and breast-fed curves until the curves merge at about the fourth month. An examination of the table shows that in each group the results are extremely close. By statistical analysis it was found that in the present series of cases the three types of feeding did not differ in their effects on the packed cell volume in the first 13 months of life.

Two sets of figures for packed cell volume, those of Drucker and those of Mugrage and Andresen, are available for comparison with the present series. In Table 3 and Fig. 3 are set out the mean values in the breast-fed group of infants and the values in Drucker's and Mugrage and Andresen's cases. As with the haemoglobin and red cell count there is a wide difference between the haematocrit values at birth as recorded by Mugrage and Andresen and the author. Mugrage and Andresen's figure, estimated on blood from the umbilical cord, was 53·18% compared with the present author's 62·65%, obtained on blood from the peripheral circulation. (Drucker did not examine any infants under three weeks of age.) At two to three months of age Drucker's value was 35·7% while Mugrage and Andresen's and the author's values were a little lower and almost identical, being 34·18% and 34·25% respectively. In Mugrage and Andresen's cases a slight rise to 37·4% at four to seven months of age was followed by a slight fall to 36·8% at 9 to 12 months. The value in Drucker's cases rose slightly after the third month to an average of 38·2% from the seventh to the twelfth month. In the present work an average of 36% remained practically constant from the fourth month onwards (Table 3 and Fig. 6). Mugrage and Andresen's haematocrit readings and those of the present series are extremely close except for the values at birth, and the great difference at this

TABLE 12

ABSOLUTE VALUES OF RED CELL CHARACTERISTICS IN ALL CASES FROM BIRTH TO 13 MONTHS

Age	Haemoglobin (G. per 100 ml. blood)	Haemoglobin (Percentage Haldane)	Red Blood cells (m.per c.mm.)	Haematocrit (%)	Mean Corpuscular Haemoglobin (γγ.)	Mean Corpuscular Volume (cμ.)	Mean Corpuscular Haemoglobin Concentration (%)	Colour Index
0–48 hours	20·7	149·6	6·60	63·25	31·4	95·8	32·7	1·13
3–7 days	19·8	143·8	6·39	59·76	31·0	93·5	33·1	1·12
8–21 ,,	18·2	131·7	5·85	54·51	31·1	93·2	33·4	1·13
22–35 ,,	15·2	110·5	5·02	44·26	30·3	88·2	34·3	1·10
6– 8 weeks	13·1	95·2	4·47	36·95	29·3	82·6	35·4	1·06
9–12 ,,	11·7	85·5	4·14	33·90	28·3	81·9	34·5	1·03
13–16 ,,	12·0	87·4	4·56	35·04	26·3	76·8	34·2	0·96
17–20 ,,	12·3	89·2	4·93	36·00	24·9	73·0	34·1	0·90
21–24 ,,	12·4	89·7	5·12	36·79	24·2	71·8	33·7	0·87
25–28 ,,	12·2	88·7	5·19	36·51	23·5	70·3	33·4	0·85
29–32 ,,	11·9	86·4	5·11	36·32	23·3	71·1	32·8	0·84
33–36 ,,	11·8	85·6	5·12	36·35	23·0	70·9	32·5	0·83
37–40 ,,	11·9	86·5	5·29	36·72	22·5	69·4	32·4	0·82
41–44 ,,	11·7	85·0	5·20	36·43	22·5	70·0	32·1	0·82
45–48 ,,	11·5	83·4	5·14	35·48	22·4	69·0	32·4	0·81
49–52 ,,	12·0	86·9	5·33	36·83	22·5	69·1	32·6	0·82
53–56 ,,	11·4	82·3	5·30	35·58	21·5	67·1	32·0	0·78

age may be due to the fact that blood from the umbilical cord was examined by Mugrage and Andresen whereas capillary blood was examined by the present author. Stasis of blood in the capillaries in the newborn is of common occurrence and may have contributed to the higher findings in the present series.

Mean Corpuscular Haemoglobin, Mean Corpuscular Volume, Haemoglobin Concentration, and Colour Index. Table 9 shows the absolute values and their derivatives of the red cell characteristics in breast-fed infants from birth to 13 months of age. Similarly, Table 12 shows the values in 'all cases.' Figs. 11, 9, and 12 are graphs of the

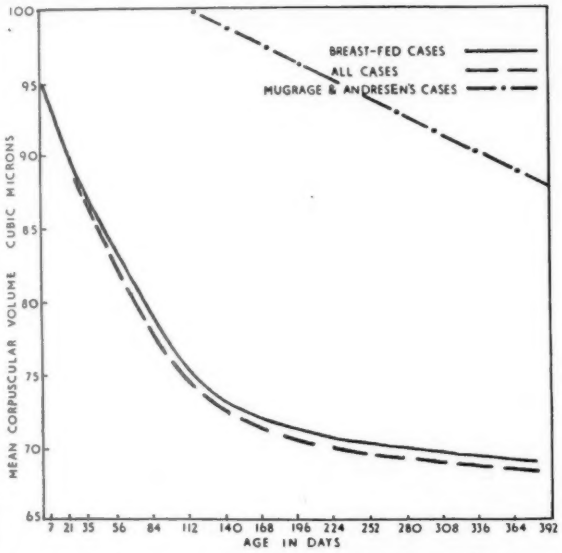

FIG. 11.—Mean corpuscular volume of breast-fed cases, all cases, and Mugrage and Andresen's cases.

changes in these derivatives in breast-fed cases and in 'all cases,' that is, in the mean corpuscular volume (Fig. 11), the mean corpuscular haemoglobin (Fig. 9), and the mean corpuscular haemoglobin concentration (Fig. 12).

In the breast-fed group the mean corpuscular volume is high, 95·8 c.μ., at birth, falls rapidly to about 73·8 c.μ. at 17 to 20 weeks, and then falls more slowly to 64·6 c.μ. at 53 to 56 weeks. The figures for 'all cases' are slightly but consistently lower over the same period. The steep fall from birth to five months coincides with the change from the macrocytosis seen at birth to normocytosis. The continued fall after the fifth month runs parallel with the tendency to microcytosis seen towards the end of the first year (Guest and Brown, 1936; Faxen, 1937). The figures for the mean corpuscular haemoglobin of breast-fed cases and of 'all cases' are a great deal lower than those recorded by Mugrage and Andreson, that is, 108·9 c.μ. in cord blood and 85·3 c.μ. from 12 to 18 months.

The values for the mean corpuscular haemoglobin of breast-fed cases and of 'all cases' show a similar but less abrupt fall to the mean corpuscular volume. The graph of the mean corpuscular haemoglobin of breast-fed cases is the same as that of the colour index (Fig. 6) and shows a steady fall from 31·3 γγ (colour index 1·13) at birth to 25·6 γγ (colour index 0·93) at 17 to 20 weeks followed by a much slower fall to 21·6 γγ (colour index 0·79) at 53 to 56 weeks. This fall coincides with the change from the hyperchromia seen at birth to the relative hypochromia of the year-old infant (Guest and Brown, 1936; Faxen, 1937).

The figures for the mean corpuscular haemoglobin concentration varied very little during the first year. They were 32·7% at birth, rose a little to 34·7% at 17 to 20 weeks, fell slightly to 32·1% at 41 to 44 weeks, and rose again to 33·4% at 53 to 56 weeks. Except for

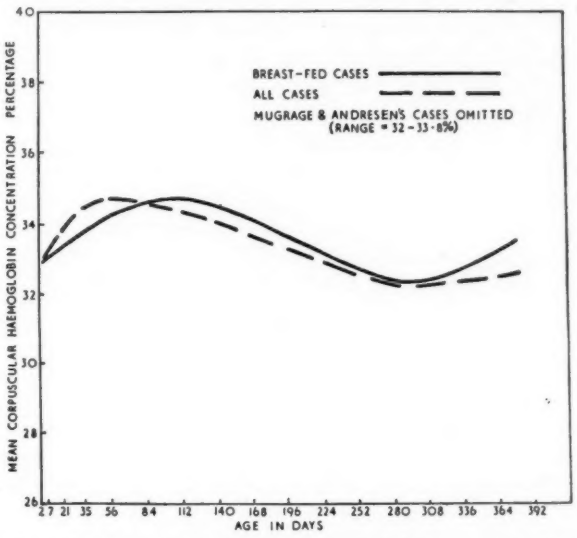

FIG. 12.—Mean corpuscular haemoglobin concentration in breast-fed cases and all cases.

the value of 34·7% at 17 to 20 weeks these figures lie within Mugrage and Andresen's range of 32 to 33·8% and are all within the normal limits for adults. The mean corpuscular haemoglobin concentration in 'all cases' did not show as great a variation as in breast-fed cases. It reached its maximum at about eight weeks, started to decline sooner and thereafter remained at a slightly lower level.

Summary

An investigation is described which attempted to establish normal values in the blood picture for infants, to account for the disparity between the findings of different workers, and to determine whether all infants should receive prophylactic doses of iron in their first year of life.

The sample consisted of 249 infants drawn from Birmingham and its suburbs. The sample racially was as purely English as could be obtained. Twins and infants weighing less than 6 lb. at birth were excluded, as also were those who had suffered any serious illness and those failing to make the expected weight gain. No infant was included whose mother had proved to be anaemic during pregnancy.

The technique used is described, and the results of approximately 1,200 blood counts analysed.

It was found that the haemoglobin curve of breast-fed infants ran parallel and close to that of other workers, and after the age of six months was practically identical with Mackay's, also working with English material. In no one age-group, however, was there any statistical difference between the haemoglobin values in breast-fed infants, artificially fed infants, or infants fed on a mixture of breast and cow's milk, but on averaging the results of all age groups it was found that the means of three methods of feeding were significantly different, the highest in breast-fed, and intermediate in cases only partly breast-fed. At 12 months of age the difference between the haemoglobin levels of artificially fed infants and those receiving iron were statistically significant, the iron-fed group having the higher figure. The differences in haemoglobin values recorded by various workers appear to be fundamentally racial.

The red cell values in the first year of life of breast-fed infants lay roughly parallel to those of Faxen, although the actual values were much higher, as also they were after the age of four months compared with those of the other workers cited. There was no statistical difference between the red cell counts in breast-fed infants, artificially fed infants, or infants fed on a mixture of breast and cow's milk.

The curve of the haematocrit values of breast-fed infants ran roughly parallel to those of the haemoglobin and red cell count.

Mean values for the haemoglobin, red cell count, and haematocrit were established at ages ranging from birth to 13 months.

Thanks are due to the medical officers of the Maternity and Child Welfare Service of the City of Birmingham Health Service for their co-operation, as, without access to children under their care at the maternity homes and child welfare clinics, this work could not have been undertaken. Thanks are also due to the Medical Research Council for defraying the expenses of this investigation; to Mr. E. A. Cornish of the Australian Council for Scientific and Industrial Research, who made a statistical analysis of the results, and to Miss N. R. McArthur, of the Walter and Eliza Hall Institute, Melbourne, for her help and advice in preparing the tables and graphs.

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PROTEIN REQUIREMENTS OF INFANTS

4—SERUM PROTEIN CONCENTRATIONS IN NORMAL FULL-TERM INFANTS*

BY

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(Received for Publication, August 18, 1949)

A number of investigators have estimated the plasma and serum protein concentrations in newborn infants and young children (Utheim, 1920; Darrow and Cary, 1933; Rennie, 1935; Dodd and Minot, 1936; Trevorrow, Kaser, Patterson, and Hill, 1941; Bridge, Cohen, and McNair Scott, 1941; Hickmans, Finch, and Tonks, 1943; Rapoport, Rubin, and Chaffee, 1943). The differences in the results which were obtained by these workers may be partly due to the fact that they employed different methods. All agree, however, that the protein concentrations tend to be lower in newborn infants than in older children and that adult concentrations are not reached until the first year of life. Trevorrow *et al.*, who obtained data from a large series of infants, have also shown that there is a fall in the total plasma protein concentrations during the first four weeks of life followed by a gradual rise to the adult concentration, which is reached by about four years of age. These changes are due to variations with age in both the albumin and the globulin fractions, which vary independently of each other.

Studies of the protein requirements of infants at the Children's Hospital, Birmingham (Young, Bishop, Hickmans, and Williams, 1949; Young, Poyner-Wall, Humphreys, Finch, and Broadbent, 1950) stimulated interest in the serum protein concentrations of infants. The present observations on normal full-term infants were planned in order to provide a basis of comparison for values obtained from sick and premature infants.

Present Investigation

Material. Two hundred and forty-five estimations of serum protein concentrations were made on samples obtained from 225 infants whose ages ranged from thirty-six hours to one year. The newborn infants were occupants of the nurseries at the Birmingham Maternity Hospital and at the Sorrento (one of the City of Birmingham maternity hospitals), and the infants aged two weeks to three months were attending the follow-up welfare clinics at these hospitals. The older group were healthy infants attending the out-patient department of the Children's Hospital, Birmingham, for minor surgical procedures, such as circumcision. Infants, who showed signs of malnutrition or had a history of infection during the preceding three months, were not included. Details regarding feeding and immunization were not obtained.

Blood for analysis was usually taken from a scalp vein but occasionally capillary blood obtained by heel prick was used. The results of estimations on samples collected by the two methods from one subject on the same occasion were always found to agree within the limits of experimental error, and therefore the two methods could be used indiscriminately in obtaining material for this investigation.

Method of Analysis. All of the serum protein concentrations in this and in the parallel investigations (Young *et al.*, 1949) were estimated by micro-Kjeldahl digestion followed by direct nesslerization (Hickmans, 1948). It has been shown that this method tends to give lower results (on average about 0·25 g. of protein/100 ml.) than are obtained by micro-Kjeldahl digestion followed by titration (Broadbent and Finch, 1950).

Results. The individual values, and the averages calculated from them, for total serum protein, albumin, and globulin concentrations in full-term infants from birth to one year are shown in Fig. 1. The exact data are given in Table 1.

It can be seen from Fig. 1 that there was a very wide range for the total serum protein, albumin and globulin concentrations throughout the first year of life. This finding confirms the observations made by Trevorrow *et al.* (1941), and also by Hickmans *et al.* (1943) for the total protein values in plasma.

The average concentrations of both the serum albumin and the serum globulin fractions during the first three months of life varied with age and these variations resulted in changes in the average concentration of total protein. The average value for the total protein concentration for the first fortnight of life was 5·65 g./100 ml. and it fell

* Part of a report prepared for the Medical Research Council's Committee on the Protein Requirements of Infants.

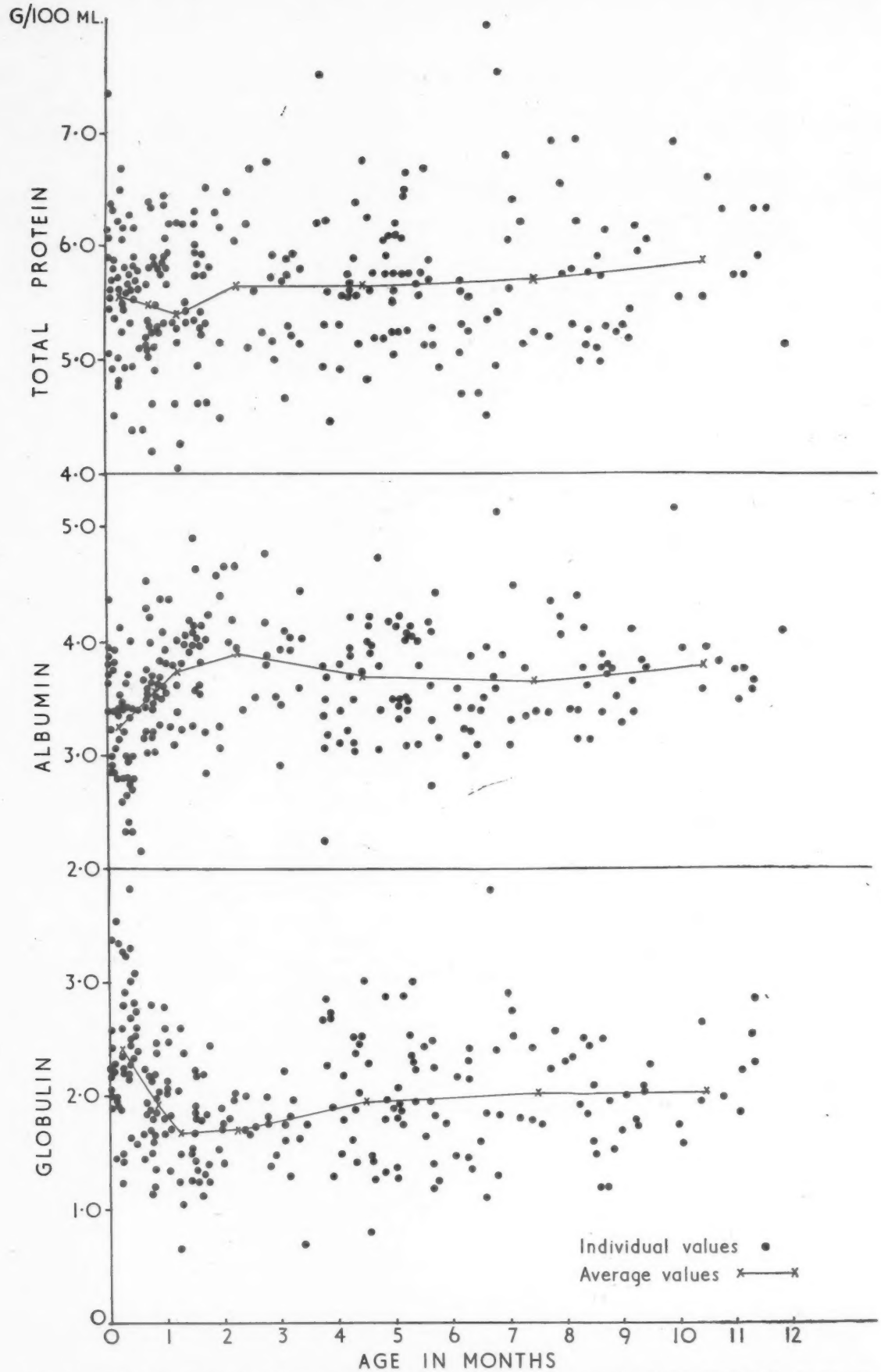

FIG. 1.—Total serum protein, albumin, and globulin (g./100 ml.) in normal infants from birth to one year. (Compare Table 1.)

TABLE 1

AVERAGE TOTAL SERUM PROTEIN, ALBUMIN, AND GLOBULIN CONCENTRATIONS FOR INFANTS FROM BIRTH TO ONE YEAR

No. of Cases	Age	Total (g./100 ml.)	Albumin (g./100 ml.)	Globulin (g./100 ml.)
46	Birth to 2 weeks ..	5·65	3·26	2·41
30	2 to 4 weeks	5·48	3·57	1·92
15	4 to 6 weeks	5·40	3·72	1·68
34	6 to 13 weeks	5·66	3·94	1·73
63	3 weeks to 6 months	5·66	3·69	1·95
40	6 to 9 months	5·70	3·66	2·02
17	9 months to 1 year ..	5·87	3·83	2·05

to 5·40 g./100 ml. between the second and sixth week, after which there was a gradual rise to the original level by the third month of life. The average value remained at this level (5·70 g./100 ml.) during the following nine months with a slight rise as the age approached one year. The average value for the albumin fraction was relatively low (3·26 g./100 ml.) during the first fortnight of life, but by the sixth week it had risen to 3·72 g./100 ml., and it remained at this level until one year of age. The average value for the globulin fraction was correspondingly high during the neonatal period (2·43 g./100 ml.), and fell to 1·68 g./100 ml. between the second and sixth week of life. It was maintained at this level until the age of three months after which there was a gradual rise to an average value of 2·00 g./100 ml. This was reached between the fourth and sixth months of life. The high average globulin and low average albumin concentrations which have been found during the first two weeks of life were partly due to a small number (nine) of very high values for the globulin fraction with correspondingly low values for the albumin fraction in most cases. These exceptional levels may have been 'true values' or they may have been due to some factor or factors in the serum of certain infants which affected the salting out procedure.

The results of plasma and serum protein concentrations in full-term infants obtained by other workers who used the micro-Kjeldahl method, and those obtained in the present investigation, have been tabulated (Table 2). Some of the data from this table have also been graphed (Fig. 2); 0·2 g. (an allowance for fibrinogen) has been deducted from the plasma values which were obtained by Trevorrow *et al.* in order to make the levels directly comparable with the other serum protein levels shown in Fig. 2. The average total serum protein concentrations of the infants in the present series compared with those

TABLE 2

PLASMA AND SERUM PROTEIN CONCENTRATIONS OF FULL-TERM INFANTS DETERMINED BY MICRO-KJELDAHL METHOD

Author		No. of Cases	Age	Total (g./100 ml.)*	Albumin (g./100 ml.)*	Globulin (g./100 ml.)*
Darrow and Cary (1933)	Serum	20	Newborn (3–10 days)	*5·52* (±0·58)	*3·73* (±0·38)	*1·78* (±0·45)
		14	150–180 days	*6·29* (±0·33)	*4·28* (±0·38)	*2·01* (±0·34)
Rennie (1935)	Serum	4	3–6 months	*7·09*	*4·75*	*2·34*
		7	6–12 months	*7·11*	*4·81*	*2·30*
Dodd and Minot (1936) ..	Serum	16	Birth—3 months	*5·44*	*3·66*	*1·78*
		34	3 months-2 years	*6·19*	*4·28*	*1·91*
Trevorrow, Kaser, Patterson, and Hill (1941)	Plasma		Birth	*5·70* (±0·45)	*3·79* (±0·33)	*1·66* (±0·29)
			4 weeks	*5·33* (±0·37)	*3·79* (±0·33)	*1·31* (±0·25)
			6 months	(6·00)		
			1 year	(6·20)	*4·70* (±0·73)	*1·38* (±0·68)
Hickmans, Finch, and Tonks (1943)	Plasma	180	Birth	4·00–7·00		
			3–12 weeks	4·70–7·40		
			Over 3 months	6·00–7·40		
Rapoport, Rubin, and Chaffee (1943)	Serum	17	Newborn (First 48 hours)	*5·11* (±0·76)	*3·76* (±0·43)	*1·34* (±0·41)
		16	2–11 months	*6·10* (±0·29)	*4·97* (±0·73)	*1·38* (±0·68)
Present investigation ..	Serum	46	Birth–2 weeks	*5·65* (±0·51)	*3·26* (±0·47)	*2·41* (±0·69)
		30	2–4 weeks	*5·48* (±0·64)	*3·57* (±0·48)	*1·92* (±0·41)
		15	4–6 weeks	*5·40* (±0·65)	*3·72* (±0·39)	*1·68* (±0·55)
		34	6–13 weeks	*5·66* (±0·63)	*3·94* (±0·55)	*1·73* (±0·77)
		120	3 months–1 year	*5·70* (±0·62)	*3·70* (±0·41)	*2·00* (±0·38)

* Shows standard deviation.

of the infants in the series of Trevorrow *et al.* show (1) a slightly higher level during the neonatal period, (2) an initial fall which is similar in degree, (3) an earlier rise, and (4) good agreement with the levels from four months to one year. Darrow and Cary obtained similar, and Rapoport *et al.* somewhat lower, average values for the newborn infants, and both groups of workers found higher average values during the later months of infancy. The present series shows uniformly lower albumin and higher globulin levels than were obtained by Trevorrow *et al.* The results obtained by Rapoport *et al.* for both fractions are similar to those obtained by Trevorrow *et al.*, but Darrow and Cary found higher globulin levels, the average of which was almost the same as that obtained from our series. The method of separation of the protein fractions seems the most probable explanations for these differences.

Discussion

The observations which have been made in the present and in previous investigations may be used as a guide to the value of serum protein determinations in young infants. It has been found that the range and distribution of the serum protein concentrations of normal infants is very wide and that a proportion of infants have values which would be regarded as evidence of a severe degree of hypoproteinaemia in older children or adults. Serum protein levels, therefore, cannot be used to assess nutritional status in individual infants during the first year of life. The range, distribution, and average levels of a series of normal infants may, however, be used as a basis of comparison for the

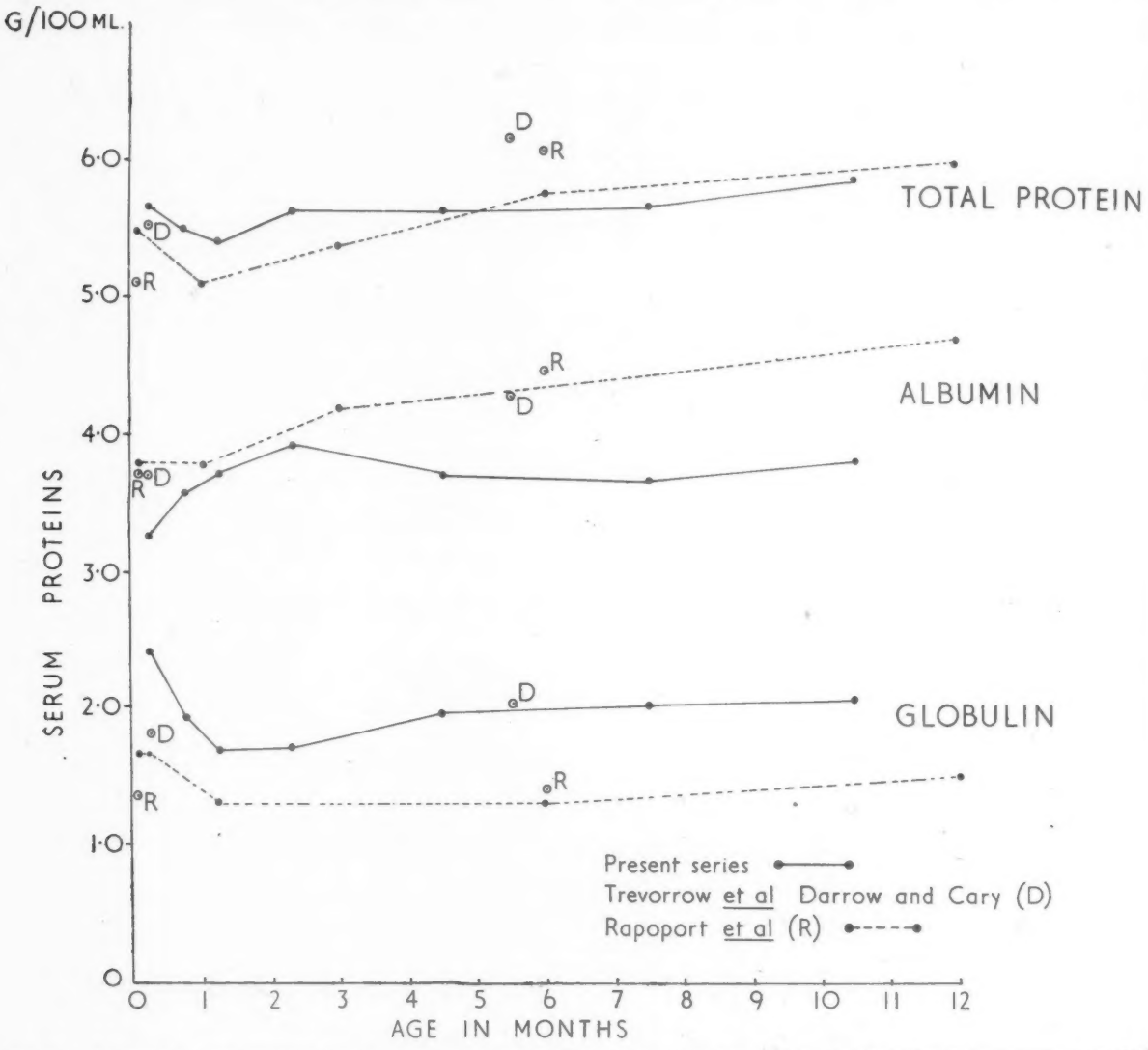

FIG. 2.—Average serum protein levels in present series compared with the levels obtained by Trevorrow *et al.* (1941), Darrow and Cary (1933), and Rapoport *et al.* (1943).

levels of a particular group of infants, in order to determine whether hypoproteinaemia has occurred more frequently amongst them (see Parts 2 and 3 of this paper).

The serum protein concentrations which are presented in this report should not be regarded as 'standard' absolute values for normal infants, since the results obtained by the method used have been found to differ from those obtained by micro-Kjeldahl digestion followed by titration, and the difference is not a consistent one. Furthermore, a survey of a much larger number of levels would be required to obtain standards of statistical value for infants during the early months of life, because the range and distribution of the levels is so wide at this age.

Summary

Total protein, albumin, and globulin concentrations have been estimated in the serum of a series of normal full-term infants whose ages ranged from thirty-six hours to one year. The levels were estimated by micro-Kjeldahl digestion followed by direct nesslerization, a method which tends to give lower results than those obtained by micro-Kjeldahl digestion followed by titration.

A very wide scatter for all three concentrations was found throughout this period of infancy. The average total serum protein levels showed a slight initial fall during the first few weeks of life followed by a rise to the original level by three months of age and a further slight rise as the age approached one year. These changes were due to variations in both the albumin and the globulin fractions.

Some of the data included in this report were obtained by Dr. A. Rothe-Meyer at the beginning of the investigation. The authors are grateful to Professor Sir Leonard G. Parsons and Professor J. M. Smellie for their helpful criticism and advice and to Dr. Frances Braid and Dr. V. M. Crosse for allowing them to examine patients under their care. P. P.-W. is also indebted to the Medical Research Council for the grant which she received during the time that this work was in progress.

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5—THE ESTIMATION OF SERUM PROTEIN CONCENTRATIONS*

BY

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(Received for Publication, August 18, 1949)

Towards the completion of the work it was realized that the results obtained by the nesslerization method described in Parts 2-4 of this series of papers tended to differ from those obtained by the micro-Kjeldahl digestion of a larger quantity of serum followed by titration (Young, Bishop, Hickmans and Williams, 1949; Young, Poyner-Wall, Humphreys, Finch and Broadbent, 1950; Poyner-Wall and Finch, 1950). It was therefore decided to compare a series of results obtained by the two methods.

Comparison of Results Obtained by Nesslerization and by Titration

Although the digestion mixture which was used for the nesslerization method was suitable for the rapid digestion of 0·005 ml. of serum, the presence of the phosphoric acid made it unsatisfactory for the prolonged digestion of 0·1 ml. of serum. This digestion was therefore carried out with a mixture of the same composition as that used by Levin, Whitehead, and Oberholzer (data to be published) so that the results from the two hospitals taking part in the Medical Research Council investigations could be correlated.

Method of Comparison. The comparison was first carried out by taking one sample of serum and repeating the estimation, by nesslerization, of the total nitrogen in 0·005 ml. of serum 28 times, i.e. on 2·5 ml. of a solution of 0·1 ml. of serum in 50 ml. of water. The total nitrogen in 0·1 ml. of the same serum was estimated four times by the titration method. For these comparative results, the total nitrogen has been converted to grammes of protein per 100 ml. but no correction has been made for the non-protein nitrogen. The results by nesslerization showed a wide scatter but the four results obtained by the titration method were all within 0·10 g. protein per 100 ml. of each other. The average of these four results, viz. 6·75 g. protein per 100 ml. has been taken as correct. Fig. 1A is a frequency distribution diagram of the differences between the individual results by nesslerization and the average of the four results by titration. It shows that 20 out of 28, i.e. 71% of the results by nesslerization were within ±0·25 g. protein per 100 ml. of the average titration value. It also shows that there were more results by nesslerization below the titration value than above it and that the biggest differences were always due to low results by the nessler method. The average of the 28 results by nesslerization was 6·53 g. protein per 100 ml. and the standard deviation of the results about this average was 0·39 g. The deviation of the results by nesslerization about the average of the titration results (6·75 g. protein per 100 ml.) was 0·45 g.

A second comparison of the two methods was carried out by making a duplicate estimation of the total nitrogen, by each method, on 71 different samples of serum. The duplicate estimations by the titration method did not vary by more than 0·13 g. protein per 100 ml. In all except three cases, the duplicate estimations by the nessler method did not vary by more than 0·20 g. protein per 100 ml. and none varied by more than 0·40 g. protein per 100 ml. The comparison has been made on the average of the duplicate estimations and the titration result has been assumed to be correct in each case. Fig. 1B is a frequency distribution diagram of the difference between the results by the two methods. Thirty-seven of the 71, i.e. 52%, of the results by nesslerization were within ±0·25 g., and 51 of the 71, i.e. 72%, were within ±0·35 g. of protein of the titration value. Although section A of the figure presents a rather different picture from section B, because in the second series there was a greater percentage of the results within ±0·05 g. of the titration value, it can be seen that again there were more results below the titration value than above it and that the biggest discrepancies were due to lower results by the nesslerization method. There was no apparent relationship between the discrepancy in the results by the two methods and the level of the serum protein being estimated.

Conclusion

The average of a series of serum protein concentrations estimated by the nesslerization method (Hickmans, 1948) was slightly lower (0·22 g. protein per 100 ml.) than the average of the same series determined by a titration method. Since the error of the

* Part of a report prepared for the Medical Research Council's Committee on the Protein Requirements of Infants.

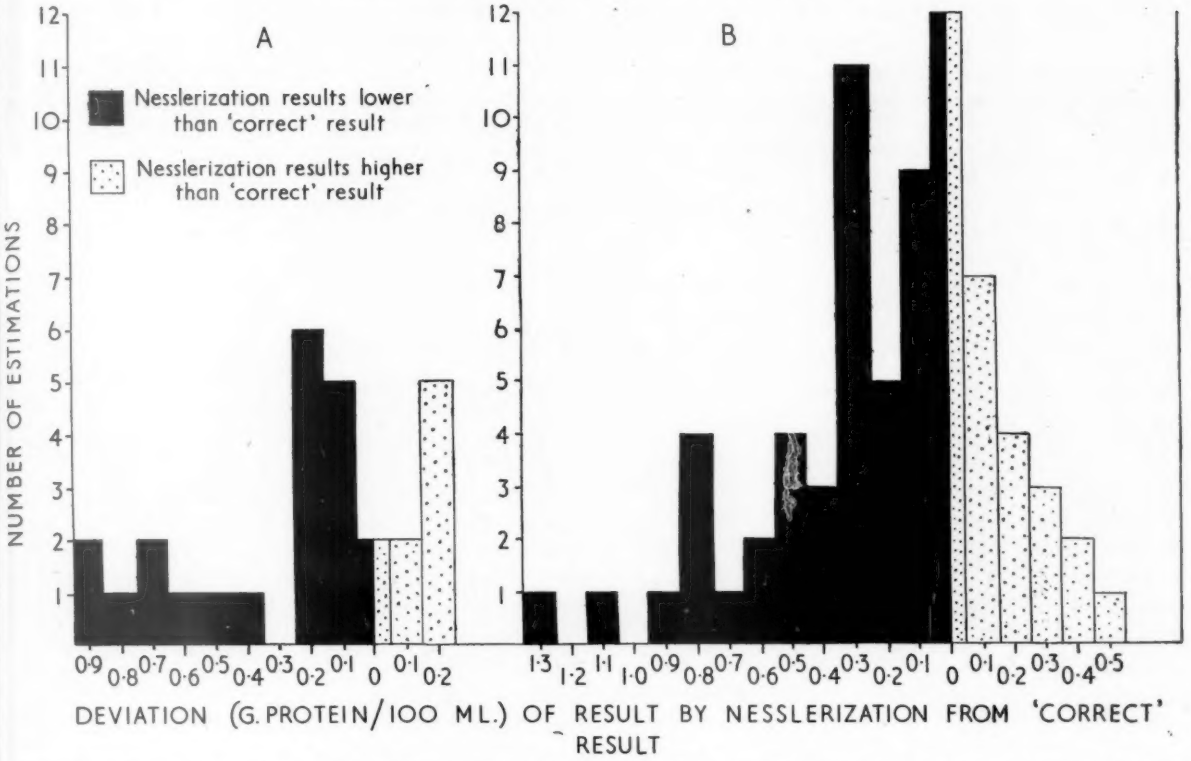

FIG. 1.—Comparison of serum protein concentrations determined by nesslerization with the 'correct' result determined by titration. A. These estimations were made on a single sample of serum. The average of four results by titration is assumed to be correct. B. These estimations were made on 71 different sera. For each sample the average of duplicate estimations by titration is assumed to be correct.

nesslerization method is not a consistent one, no correction can be applied to individual results which have been obtained by this method. If, however, the serum protein concentrations of a sufficiently large number of cases have been estimated, the effect of individual errors on the average of the results is reduced and it is possible to assess the findings. Nevertheless, when small variations in serial specimens are to be estimated, the titration method is preferable in spite of the fact that it requires a little more serum.

The authors wish to thank Dr. E. M. Hickmans for advice and criticism. I.B. is indebted to Messrs. Cow and Gate for a research fellowship from the Department of Paediatrics and Institute of Child Health of Birmingham University.

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INFANTILE DIARRHOEAL DEHYDRATION TREATED WITH ADRENAL CORTICAL HORMONE AND POTASSIUM CHLORIDE*

BY

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(RECEIVED FOR PUBLICATION, OCTOBER 4, 1949)

Dehydration is the danger signal of infantile diarrhoea because without dehydration the mortality from properly treated gastro-enteritis should be negligible, hence the importance of preventing dehydration and the recognition that its presence indicates a medical emergency. Important constituents of both extracellular and intracellular body fluids are the electrolytes, and Gamble (1947) considers the term 'dehydration' incomplete because it fails to indicate, as was shown by McIntosh, Kadji, and Meeker (1931), that water loss is always accompanied by loss of electrolyte. It follows that therapeutic repair cannot be effective unless both water and electrolyte are replaced.

Electrolytes are dissociated within the body; for example, sodium chloride is present as separate sodium ions and chloride ions. With diarrhoea there is an excessive excretion of water, protein, chloride, sodium and bicarbonate ions (mainly extracellular electrolytes), and potassium and magnesium ions (mainly intracellular electrolytes). Over 30 years ago Holt, Courtney, and Fales (1915) showed that diarrhoeal stools contain much larger amounts of water and electrolyte than do normal stools, and they expressed the view that a better solution than the Ringer's and normal saline then in use could be devised for parenteral therapy. Prolonged electrolyte loss produces dehydration (Gamble, 1947; Darrow, 1944; Darrow, 1947a); this was confirmed experimentally in animals by Darrow and Yannet (1935). Until recently the cell membrane was believed to be impermeable to the passage of electrolyte and that therefore only extracellular electrolyte could be replaced. Darrow and others found, however, that potassium and sodium do penetrate cell membranes. This led to the introduction by Darrow of his sodium-potassium-chloride solution as a therapeutic measure for the replacement of intracellular as well as extracellular electrolyte (Govan and Darrow, 1946; Butler *et al.*, 1946).

The acidosis which so commonly accompanies diarrhoeal dehydration is a chloride acidosis (Hartman, 1928; Hamilton *et al.*, 1929). This is associated with a fall in blood bicarbonate and a loss via the stools of a fixed base, i.e. sodium, potassium, calcium, and magnesium (Hoag and Marples, 1931). It is possible that a decrease of cellular potassium may contribute towards acidosis since it is known that the depleted potassium tends to be replaced within the cells by sodium, leaving an excess of chloride ions in the extracellular fluid (Darrow, 1947a). Rapoport and Dodd (1947) stress the importance of giving calcium in the post-acidotic phase. There is no indication that magnesium needs replacing.

Regulation of sodium and chloride metabolism and water balance is a function of the adrenal cortex hormone, and desoxycorticosterone is the active principle (Grollman, 1939). The adrenalectomized animal loses body fluid, sodium, and chloride (Harrop, Soffer *et al.*, 1933; Harrison and Darrow, 1938), and administration of cortical extract reverses this process although large doses may cause a fall in the serum potassium level. Synthetic desoxycorticosterone has a similar effect (Clinton and Thorne, 1943; Thorne and Firor, 1940; McCullagh and Ryan, 1940) but in addition, toxic symptoms may appear with excessive dosage. Both of these unfavourable effects are minimized however if the subject receives a diet of liberal potassium and low sodium content (Talbot, 1948; Gordon, 1940). Selye (1947) points out that unlike desoxycorticosterone acetate, the natural hormone may be given in very large doses without fear of overdosage phenomena.

The literature contains comparatively few references to the use of the cortical hormone as an hydrating agent. Jaudon (1946; 1948) believes that physiological adrenal insufficiency occurs not

* A paper read at the 37th South African Medical Congress, Cape Town, in September, 1949.

uncommonly in the young infant and he has shown that such babies improve with adrenal hormone therapy. Collis and Majecodunmi (1943) state that the hormone is of value in dehydration with ketosis; Miller (1941) found that the physiological weight loss of the newborn infant was less after the use of synthetic cortical extract. In diarrhoeal dehydration, symptoms and blood changes occur which are similar to those seen in adreno-cortical hypofunction (Sullivan, Maclean, and Zwemer, 1932; Aldridge, 1941a). MacLean and his co-workers (1932) consider suprarenal insufficiency to be an aetiological factor in the production of acute intestinal intoxication. Hislop (1938) believes that in marasmus there is ultimately an adrenal hypofunction.

From the literature it would appear that the dehydrated infant should react favourably to adrenal or synthetic desoxycorticosterone and that potassium, apart from its replacement and possible anti-acidotic value, may be a safeguard where the cortical hormone, and especially its synthetic equivalent, is being administered.

The purpose of this paper is to record the result of certain treatments, with special reference to the action of suprarenal cortex extract as an hydrating agent, on a series of 83 infants suffering from diarrhoea with dehydration. The subjects of this investigation were coloured and native babies, and the work was carried out at the Victoria Hospital, Wynberg. Much of the clinical material was of poor quality; because of parental poverty and ignorance many of these infants were malnourished and debilitated before the onset of the diarrhoea for which they were admitted to hospital. All were dehydrated, many severely so, and quite a number had symptoms of toxaemia as well.

Therapeutic Plan

A basic scheme included treatment with the following preparations, and a graduated scheme of feeding.

Extract of Adrenal Cortex. 'Adrocortin'* (Saphar Laboratories) was the preparation used; each ml. corresponds to the hormone activity of 50 g. of the fresh gland. Therapeutic units of 2 ml. were given intramuscularly once or twice daily depending on the severity of the case. A few special cases received three injections per day.

Sodium-Potassium-Chloride ('Darrow's') Solution. Darrow's formula (1947b) was concentrated for convenience to:

Sodium chloride, 32 g.; potassium chloride, 21·6 g.; sodium bicarbonate, 35·2 g.; water to 1 litre. One tablespoonful (½ oz.) of this mixture was added to each pint of 5% glucose solution.

Feeding. It was considered advisable to use milk of reduced fat content in order to counteract fat intolerance. 'Dryco,'† a powdered milk, was the product used in this instance. Liquified 'Dryco' of full strength obtained by dissolving one part in seven parts water, has the following composition:

Fat, 1·5%; protein, 4%; lactose, 5·7%; mineral salts, 0·9%; water, 87·9% (manufacturer's analysis).

Fluid Replacement and Milk Mixtures. In the basic scheme fluids were given orally, and to make up the fluid already lost 3 to 3½ oz. per lb. body weight per day was the standard aimed at. During the first 24 hours of treatment Darrow's solution only was given. Then the infant received a 'Dryco' mixture, five feeds per day, at the usual four-hourly intervals. As it was considered preferable not to use very weak milk mixtures (Emdin, 1948), the initial 'Dryco' mixture was of half-strength with 4% carbohydrate added in the form of dextri-maltose. Of this the baby was offered 2 oz. per feed if under 8 lb. in weight, and 3-4 oz. if above this weight, the fluid deficit being made up by giving Darrow's solution between feeds. With progress, the quantity of each feed was increased to 4 oz. for the lighter and 6 oz. for the heavier baby. In the second stage of dietetic treatment, the mixture was changed to two-thirds of the full strength, and later 'Dryco' was replaced by a mixture of two-thirds cows' milk and one-third water; 4% carbohydrate was added in each instance. The milk mixtures were not acidified. Finally the cows' milk formula was adjusted in accordance with the infant's age, and where indicated, the diet was completed by giving cereals, vegetables, etc. Darrow's solution was continued for two weeks, being then replaced by 5% glucose in water. Vitamins were offered in the second week of treatment.

The subjects under review were graded clinically on a basis of dehydration into mild and severe cases, the severely dehydrated babies being further classified into (*a*) cases showing little or no symptoms of toxicity, and (*b*) those in which intestinal intoxication was present or became established later. For the purpose of treatment the 83 cases were divided into two groups. To Group 1 (49 patients), the therapeutic scheme was applied. Group 2 (34 patients) was used for comparison with certain cases in Group 1; these infants received the same mineral salts and milk mixtures as the babies of Group 1 but 'Adrocortin' was omitted from the treatment scheme (with certain exceptions) and in addition, the very toxic patients were given parenteral fluids by the intravenous route. The infants who developed complicating infections such as bronchitis, pneumonia, otitis media, abscesses, etc., were treated with penicillin where necessary. Sulphonamides were not used.

Results of Treatment in Mild Dehydration

Group 1: Basic Therapeutic Scheme Applied (11 Cases). These infants were in much better condition than the

* The author is indebted to Messrs. Saphar Laboratories, Ltd., of Johannesburg, for their generosity in supplying the 'Adrocortin' used for this investigation.

† The Borden Co.

severely dehydrated babies to be described later, but nevertheless, all showed evidence of dehydration, such as loss of tissue turgor and skin elasticity (especially on the lower abdomen and thighs), depressed fontanelle, dry mouth and tongue, thirst, oliguria, etc. The body weights averaged one-third less than the normal weights for age, and in most cases diarrhoea and vomiting had begun from four to seven days before admission. Five of these babies had symptoms of mild toxaemia: coldness of the extremities, irritability, restlessness, periodic bouts of purposeless crying; two patients exhibited a tendency to stare fixedly.

The babies did well and fluids were taken eagerly from the start. 'Adrocortin' was administered once daily to seven of these infants and twice daily to four. The shortest period for which the hormone was given was three days and the longest, twelve days. The arithmetical average was six days. Response to treatment was immediate and satisfactory. By the third day the babies were more active and contented, food and fluids were taken well, vomiting had ceased. Relapse occurred in one case and this coincided with an attack of bronchitis; the diarrhoea was quickly controlled by Darrow's solution and 'Dryco.' There were no deaths.

The most striking change for the better was noted where toxic symptoms were present. In these cases all signs of toxicity had disappeared after only 48 hours' treatment. The babies rapidly became vigorous and active and there was clinical evidence of fluid fixation in the body.

Group 2: 'Adrocortin' Omitted from the Basic Scheme (11 Cases). These babies were of the same type as those described above and four of them exhibited symptoms of commencing toxaemia. Although there was little difficulty with Darrow's solution, the feeds were taken more reluctantly by this group than was the case where the adrenal hormone was being administered. All recovered and only two cases relapsed. In these infants compared with those in Group 1 the response to treatment and the clinical improvement was slower at first and the recovery phase was more protracted. The difference in therapeutic response was most evident in the toxic cases. With hormone therapy, the toxic symptoms were alleviated within 48 hours, whereas without 'Adrocortin' several days elapsed before a parallel degree of improvement was attained.

Results of Treatment in Severe Dehydration

In studying the effects of treatment on 61 babies with severe diarrhoeal dehydration, special attention was given to the action of the suprarenal cortical hormone. Almost every child in this series was grossly under weight, the average weight for age being 60 to 55% of the normal. Most of the cases on 'Adrocortin' received two injections a day for 10 to 14 days.

Group 1(a): No Toxicosis (21 Cases). These babies were treated in accordance with the basic therapeutic scheme. Two to four days after the beginning of treatment there was evidence of fluid replacement. Dryness of the mouth and tongue had been alleviated, the babies were lively and cheerful, and the subcutaneous tissues began to fill out: first the lower abdomen, then the face, and lastly the tissues of the thighs. Vomiting was mild and soon disappeared. Transient setbacks occurred in a few of these patients but most of them continued to improve and gained weight gradually but steadily. Two babies in this group died. One succumbed to bronchopneumonia after complete recovery from the diarrhoea, and the other died suddenly four days after admission to hospital. Permission for a necropsy in the latter case was refused.

The clinical impression was that the cortical hormone played an important part in reversing the process of dehydration. The following table records the gain in weight after four weeks of treatment of 11 malnourished and dehydrated babies with acute diarrhoea in that vulnerable age period, the first six months of life. The general improvement was more striking than the gains in weight would indicate.

TABLE

GAIN IN WEIGHT OF ELEVEN DEHYDRATED BABIES WITH DIARRHOEA

Case No.	Age on Admission (months)	Weight on Admission	Weight after 4 Weeks of Treatment
1. B.F.	2½	7 lb. 7 oz.	8 lb. 5 oz.
2. M.M.	3	5 lb. 11 oz.	*6 lb. 6 oz.
3. E.M.	3½	6 lb. 14 oz.	8 lb. 10 oz.
4. H.S.	3½	6 lb. 1 oz.	8 lb. 4 oz.
5. F.B.	3½	7 lb. 8 oz.	9 lb. 15 oz.
6. G.A.	4	7 lb. 14 oz.	9 lb. 7 oz.
7. J.E.	5	6 lb. 11 oz.	8 lb. 5 oz.
8. N.A.	5½	8 lb. 4 oz.	9 lb. 2 oz.
9. H.M.	6	8 lb. 2 oz.	9 lb. 0 oz.
10. E.W.	6	7 lb. 2 oz.	8 lb. 12 oz.
11. I.S.	6	8 lb. 2 oz.	9 lb. 13 oz.

* Ten days later this infant weighed 7 lb. 2½ oz.

Group 1(b): Toxicosis Present (17 Cases). Symptoms of intestinal intoxication ranged from extreme irritability to drowsiness, stupor, fixed stare, head retraction, and other manifestations similar to those seen in disease of the nervous system. The infants in this group were difficult to manage. Fluids and feeds were taken badly and some of the infants had to be fed by pipette or tube. The greater the initial toxicity, the more frequent were the setbacks and difficult periods. With patient nursing, however, these babies could be coaxed to take fluids and the milk mixture. Vomiting was a constant feature and when persistent became a problem of importance.

In spite of these difficulties, some degree of improvement occurred in most of these babies, but only after four or five days of treatment. Three of the babies, after the usual hesitant beginning, picked up well and made uninterrupted recoveries. The remainder, however, exhibited a tendency to retrogress, and even where the eventual outcome was satisfactory there were times when anxiety was felt regarding the immediate prognosis. Four patients, after initial improvement, had a relapse of such severity that fluids were given intravenously as

an emergency measure; these cases are included in the next section of this work. There were seven deaths.

It was evident that some measure of rehydration was taking place. Even where death occurred the final episode was almost invariably preceded by a stage of temporary betterment.

The following records indicate that toxic cases may benefit when the hormone is given in larger dosage:

CASE 12. M.B. Four days' history of vomiting and diarrhoea with loss of 2½ lb. in weight. On admission: age, 10 months; weight, 13½ lb. Vomiting became uncontrollable and therapy was apparently ineffective. Injections of the hormone were increased to three a day; vomiting became less frequent and ceased three days later.

CASE 13. F.M. On admission: age, 9 months; weight, 10¼ lb. After initial improvement, severe toxic symptoms appeared. Three hormone injections per day were given instead of two, with immediate improvement. Five days later ' Adrocortin ' could be discontinued.

CASE 14. B.K. On admission: age, 15 months; weight, 16 lb. On the third day the child became very toxic. ' Adrocortin ' was increased to three injections per day. There was rapid amelioration of symptoms and disappearance of dehydration.

CASE 15. I.J. On admission: age, 3 months; weight, 5 lb. Very dehydrated; moderately toxic. Temporary improvement on two injections of hormone; gain of 10 oz. in ten days. Sudden relapse with the appearance of severe toxic symptoms and drop in weight to 5 lb. Dosage of ' Adrocortin ' was increased to 6 ml. per day with good results. One month later the infant weighed 7 lb.

CASE 16. F.L. On admission: age, 14 months; weight, 14¼ lb. Moderately toxic. Two days later severe toxic symptoms appeared and the weight became 12¾ lb. Hormone injections were increased to three per day. At first there was little change, but four days later the toxic symptoms began to recede. The weight rose rapidly and 12 days after admission it was 15 lb. 6 oz.

All these patients made a good recovery. In each case the retrogression was of such severity as to warrant the introduction of parenteral fluid therapy. Instead, the dosage of hormone was increased, apparently with good effect. It should be noted, however, that these five cases differed from the others in this group in that at first toxic symptoms were only moderately severe, becoming aggravated later.

Group 2: Intravenous Fluids (23 Cases). In order to assess the degree of hydration effected by hormone therapy in severe diarrhoeal dehydration without toxic symptoms, the therapeutic scheme minus ' Adrocortin ' could have been applied to controls. Experience teaches that the reliance upon oral fluids without additional measures for combating dehydration in marasmic diarrhoea is likely to result in a high death rate. Such controls were not used because of the risks involved, particularly as the clinical results in the non-toxic infants were proving so informative.

Where the basic scheme was applied to infants with alimentary intoxication, however, the results were not so promising. It was decided therefore to compare rehydration resulting from hormone therapy plus oral fluids, with that following parenteral replenishment of body fluids. The adopted parenteral method was transfusion by intravenous drip of normal saline and 5% glucose in water (Levine, 1945). As the chloride content tends to be high in dehydration (Aldridge, 1941b), saline was given in restricted quantity for the purpose of replacing sodium. It was found that, as others have reported (Rapoport and Dodd, 1946), the drip may be continued for several days, with safety and profit to the child. Where indicated, small serum or blood transfusions were given as well, but only after the acute dehydration had been relieved. In addition, these infants were offered Darrow's solution by mouth and ' Dryco ' feeds.

All except eight cases in this group, four of the eight being transfers from Group 1, were admitted with advanced toxaemia. Generally speaking, the response to intravenous fluid therapy was prompt, although not necessarily sustained, and there was rapid amelioration of the toxic symptoms. Compared with similar cases in Group 1, feeds were taken sooner and more readily. Where the feeds were refused or vomiting persisted, the transfusion was of particular value. Some of these babies, apparently progressing favourably while being transfused, began to retrogress as soon as the drip was discontinued. For this reason, it was found advisable to extend rather than to curtail the infusion period. Although three to five days of transfusion was adequate for most cases, the drip was administered for as long as 13 days where necessary. The most important difference between parenteral fluid and hormone rehydration was the greater rapidity with which dehydration was relieved and toxic symptoms were alleviated when the intravenous route was used. Direct replacement of fluid appeared to be the method of choice for the immediate treatment of alimentary intoxication. Eight deaths occurred.

In the post-toxic phase, two problems arose (1) the tendency to dehydration as soon as the drip was discontinued, and (2) failure to gain weight. The following cases indicated that the suprarenal hormone may convert hydrolability into hydrostability:

CASE 17. L.M. On admission: age, 8 months; weight, 14½ lb.; very toxic. After three days of transfusion the drip was discontinued. Dehydration recurred. A second transfusion was given for three days and then stopped. Again the infant retrogressed. At this point ' Adrocortin ' was administered; there was immediate improvement with no further loss of fluid.

CASE 18. E.D. On admission: age, 3 months; weight, 8 lb.; very toxic. On intravenous drip for seven days. Although the infant's condition improved, the weight remained stationary during the next 14 days. Adrenal hormone was now given; the weight gradually increased and six weeks later the child was discharged, weighing 9 lb.

CASES 19 AND 20. The two cases were similar. Infants M.S. and A.M. on admission were 15 months old and weighed 15 and 15½ lb. respectively. Both toxic; A.M., semi-comatose. Both improved with parenteral fluids; M.S. was on the drip for seven days, and A.M. for

13 days. The body weight remained stationary after initial small gains. 'Adrocortin' was then administered. Three weeks later, the one child weighed 16 lb. 9 oz., and the other 17 lb.

Discussion and Conclusions

There are paediatricians who advocate prolonged fasting in the first stage of the treatment for gastro-enteritis. In my opinion, the marasmic infant should not be deprived of food for longer than 24 or at the most 48 hours, because this type of baby is already severely malnourished and continued starvation must further weaken the infant's resistance. Recent work by Chung and Viščorová (1948a; 1948b) indicates that food restriction is unnecessary in the treatment of infantile diarrhoea. The use of milk mixtures equivalent to not less than half-strength cows' milk proved to be satisfactory; carbohydrate may be added but it is advisable to reduce the fat because a mixture with a high fat content is likely to aggravate the diarrhoea.

Darrow (1947a; 1948) and Donaldson (1947) report that clinical improvement follows the oral or parenteral administration of potassium chloride to babies with gastro-enteritis. As regards the present investigation, the only cases from which conclusions could be drawn in this connexion were the 11 mildly dehydrated infants of Group 2, as these babies were given Darrow's solution and 'Dryco' only. These patients did exhibit a state of well-being superior to that usually seen in similar cases treated without potassium. Further, I have used potassium chloride in the treatment of over 100 cases of infantile diarrhoea without dehydration; compared with controls of 5% glucose solution, the general condition and stools of these babies improved much more rapidly and there were fewer relapses (unpublished work). Potassium by mouth is safer than by injection because of the danger of cardiac embarrassment when the serum potassium is too high. No symptoms of intoxication were noted when potassium was given orally for 14 days; in fact none appeared, when it was continued experimentally for a month in a few cases. Darrow's solution was taken eagerly on the whole, and more readily than glucose solution.

The adrenal cortical hormone is a powerful hydrating agent. It is valuable as a therapeutic measure in diarrhoeal dehydration, especially in the acute form with commencing toxicosis. In marasmus its rehydrating action is gradual but nevertheless effective, provided that severe toxic symptoms are absent. Where there is alimentary intoxication, fluid fixation through the medium of the cortical hormone is too slow; in such cases fluids should be administered parenterally. Although five very toxic infants recovered when given larger doses of hormone, one is not justified in assuming on such few cases that even massive hormone therapy is necessarily a substitute for parenteral fluids, especially in intestinal intoxication where prompt rehydration is so urgent a matter. The hydrostabilizing effect of the hormone may be utilized to promote gain in weight or to complete the process of rehydration where parenteral fluid therapy alone has not been entirely successful. In this investigation it was found that 2 to 6 ml. per day of the cortical extract was sufficient to promote adequate hydration when given for 10 to 14 days in severe cases and for half that period in mild cases.

Summary

This paper reports on the value of adrenal cortical extract and other measures in the treatment of infantile diarrhoea with dehydration.

Eighty-three cases are reviewed. The degree of dehydration varied; some of the infants had toxic symptoms in addition.

Potassium chloride solution was given orally with good effect.

Dietetically, it is recommended that after a short fasting period, milk mixtures of low fat content be offered.

The suprarenal cortical hormone is valuable for treating dehydration and for promoting gain in weight. Where intestinal intoxication is present, however, parenteral fluids should be given immediately; later, the adrenal hormone may be administered in order to promote fluid fixation in the body.

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RETICULOENDOTHELIAL GRANULOMA: A REVIEW WITH A REPORT OF A CASE OF LETTERER-SIWE DISEASE

BY

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(RECEIVED FOR PUBLICATION, FEBRUARY 3, 1950)

Granulomatous lesions affecting the reticulo-endothelial system produce a group of disorders having certain striking clinical features. The condition known as Hand-Schüller-Christian disease is one of this group, and the well-known Schüller-Christian triad of exophthalmos, diabetes insipidus, and multiple lesions in the skull was for many years considered to be pathognomonic. More recently Otani and Ehrlich (1940) and Lichtenstein and Jaffe (1940) have described a condition which has come to be known as 'eosinophilic granuloma of bone.' Multiple skeletal lesions may be present, but there is, as a rule, little evidence of systemic upset and recovery is the usual outcome. The rarest and most severe condition in this group is that known as Letterer-Siwe disease. It affects infants, frequently within the first six months of life, and invariably proves fatal.

Farber (1941) and Green and Farber (1942) have suggested that the underlying pathological changes in eosinophilic granuloma of bone are similar to those in Hand-Schüller-Christian disease and in Letterer-Siwe disease. Jaffe and Lichtenstein (1944) agreed with this concept and believed that the three conditions were 'different clinical expressions of the same basic disorder'. On the other hand, Siwe (1949) is unwilling to be so definite. He admits that they are all diseases of the reticuloendothelial system but does not feel justified in assuming that anything more than a family relationship exists.

The following case is an example of the acute form of reticuloendothelial granuloma known as Letterer-Siwe disease.

Case Report

Clinical Findings. The patient was a female infant, the second child of healthy, unrelated Gentile parents. She was born spontaneously at term on February 22, 1949, and weighed 6¾ lb. at birth. She made normal progress until, at the age of 14 weeks, she became listless and vomited her feeds. She appeared to recover but two and a half weeks later she developed diarrhoea which was treated by a course of sulphonamides. The child had little appetite and became very irritable but the diarrhoea ceased. The mother thought the infant was teething but the doctor noticed that she was becoming very pale and sent her to hospital. She was admitted on August 2, 1949, aged 22 weeks, six weeks after the onset of symptoms. The patient was a very fretful, quite well-nourished baby weighing 11 lb. 4 oz. The skin and mucous membranes were pale; there was no clinical icterus. The two lower central incisors had erupted. A few shotty glands were felt in the left groin.

The spleen was enlarged and was palpable 2 in. below the costal margin. It was smooth, firm, but apparently not tender. The liver was palpable. There was considerable disturbance in temperature (Fig. 1). No other

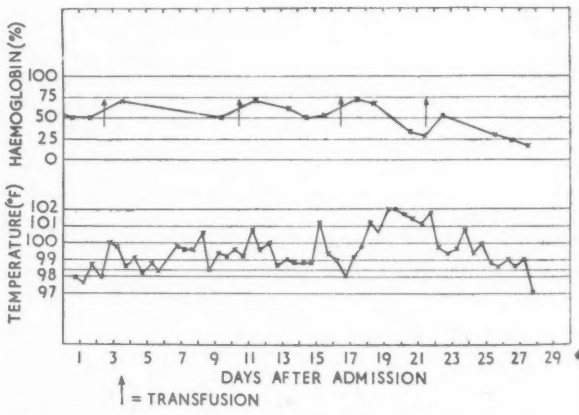

FIG. 1.—Chart showing temperature and haemoglobin.

clinical signs were present. The haemoglobin levels were estimated by the Sahli method (14 g.=100%), and indicated the progressively severe anaemia (Fig. 1). The anaemia was uninfluenced by transfusion.

The parents' and child's blood were Rhesus positive. The Wassermann reaction and Mantoux test (1/1,000) were negative. No pathogenic organisms were isolated from the stool. The blood cholesterol level was 125 mg. %.

FIG. 2.—Radiograph of skull; multiple defects in calvarium.

Cerebrospinal fluid, obtained by lumbar puncture, was normal. Urine analysis was normal. The results of the liver function tests were: serum thymol turbidity, 6 units; serum gold sol, 1; serum cephalin cholesterol flocculation, + + ; serum alkaline phosphatase, 11 units; serum bilirubin, 1 mg. %.

Frequent attempts to obtain bone marrow were unsuccessful.

Radiological Examination. Radiographic examination of the skull revealed numerous areas of rarefaction in the calvarium (Fig. 2). These areas were circular in outline and varied considerably in size. The defects gave the skull the 'map-like' appearance which has been described in Letterer-Siwe disease.

Radiographs of the lower limbs showed cyst-like defects in the lower ends of the femora and in the upper ends of the tibiae (Fig. 3). In addition to these lesions, the femoral shafts were unduly broad and the cortex was rather dense. This suggested that subperiosteal formation of new bone had occurred.

X-ray examination of the chest was negative.

Since admission, the liver, spleen and lymph nodes had increased slowly in size (Fig. 4). Sixteen days after admission a purpuric rash appeared over the trunk, neck, and limbs, and persisted for three to four days before fading.

Blood transfusions of 120-180 ml. each were given on the third, eleventh, seventeenth, and twenty-third days after admission. These caused only transient improvement (Fig. 1).

The baby died on August 29, 1949, 28 days after admission and ten weeks after the onset of the disease.

The clinical diagnosis was Letterer-Siwe disease.

Necropsy Report. The body was that of a rather small, extremely pale infant aged six months and weighing 9 lb. 10 oz. The skin over the chest was wrinkled and there was little subcutaneous adipose tissue. No skin lesions were found. The abdomen was distended, and the liver and spleen were easily felt.

HEAD. The skull showed numerous circular, semi-translucent areas over the vault of the skull and in the temporal and occipital bones. They varied in size, the average diameter being 0·5 cm. The larger lesions were yellowish in colour and soft, almost gelatinous. The brain showed no abnormality. The pituitary fossa was of normal size. The pituitary gland was normal.

THORAX. The pharynx, oesophagus, and thyroid gland showed no abnormality. The thymus gland was enlarged and firmly adherent to the surrounding tissues. The gland was irregularly shaped and on section showed numerous yellow, pultaceous areas. The trachea and bronchi were healthy. The lungs were well-expanded and reddish-pink except for the lower lobe of the right lung which was dark purple and unusually firm. There was no pneumonia. The pericardium was healthy. The heart was normal in size, but the myocardium was extremely pale. There were no congenital lesions. The coronary arteries were healthy.

ABDOMEN. The peritoneum was healthy. No abnormalities were found in stomach, small or large intestine. The liver was enlarged and weighed 226 g. The capsule was smooth and the organ was pale yellow-brown. Numerous areas of fatty degeneration were seen on the cut surface. The gall bladder and bile ducts were healthy.

FIG. 3.—Radiograph of lower limbs. Defects in lower ends of femora and upper ends of tibiae.

FIG. 4.—Patient 26 days after admission. Note enlargement of liver, spleen, and inguinal lymph nodes.

At the porta hepatis there was a group of enlarged lymph nodes which were pale yellow and rather soft. The spleen was greatly enlarged and weighed 126 g. The capsule was thickened and partly adherent to the lateral abdominal wall. The organ was firm. On section the pulp was dark red and the Malpighian bodies were prominent. The suprarenal glands and pancreas appeared to be healthy. The kidneys were of average size and shape. On section no abnormality was found. The ureters and bladder were healthy. The inguinal lymph nodes were enlarged and soft.

SKELETON. In addition to the changes in the skull, all the ribs showed areas of rarefaction, which were largest just lateral to the costo-chondral junction, and in a few cases the cortex of the rib had been expanded into a fusiform swelling 2 cm. in length. On section they were seen to consist of a gelatinous, semi-fluid mass of yellow material. The left femur also showed circular, punched-out areas, 0·5 cm. in diameter, which contained yellowish, gelatinous material similar to that found in the ribs. The lesions were primarily situated in the cancellous bone but some erosion of the cortex had also occurred. Similar lesions were found in the sternum.

Microscopy Report. The capsule of the liver was normal. The liver cells, particularly those in the inner zones of the lobules, showed severe fatty change. In addition to the fatty degeneration, numerous small granulomas were found throughout the parenchyma. These varied slightly in size but the average was that of a miliary tubercle. They were not encapsulated but the surrounding liver cells were compressed to form a pseudo-capsule. The granulomas were composed of large, pink-staining reticuloendothelial cells surrounded by a few lymphocytes and plasma cells. The central part of the lesion was, in some cases, undergoing hyalinization. Sections stained with Scharlach red showed that the lesions contained no fat although the surrounding liver cells were filled with fat droplets (Fig. 5).

The capsule of the spleen was slightly thickened. The trabeculae were normal. There were numerous granulomatous areas throughout the pulp. These areas were similar in character to those in the liver but were larger, more numerous, and less discrete. Many of the Malpighian bodies had been partially replaced by granulomatous tissue. The granulomas were composed of pink-staining reticuloendothelial cells, lymphocytes, plasma cells, and a few eosinophil leucocytes. Some of the larger granulomas showed central necrosis. They contained no fat.

Large portions of the thymus gland had been replaced by granulomatous tissue similar to that already described, but in addition to pale reticuloendothelial cells a number of giant cells were seen (Fig. 6). A few eosinophil leucocytes were also found. Many of the granulomatous areas had undergone necrosis and at the periphery of the gland replacement fibrosis had occurred. Sections stained with Scharlach red showed that many of the histiocytes in the granulomatous areas contained fat but this was almost confined to the cells in the margins of the necrotic areas.

The capsule of the lymph node was normal. The node had been largely replaced by granulomatous tissue (Fig. 7). These lesions were more discrete than those found in the spleen and thymus, and necrosis was not a pronounced feature.

The pleura was healthy. The lungs were well expanded, and the bronchi were healthy. Numerous granulomatous areas were found throughout the interstitial tissue (Fig. 8), and bore a superficial resemblance to miliary tubercles. A number of small lesions had coalesced to form larger granulomas of which a few were undergoing fibrosis. Many of the surrounding alveoli contained histiocytes.

Sections from the skull, ribs, and sternum showed similar changes. The bone had been partially replaced by granulomatous tissue which consisted of sheets of pale-staining histiocytes together with small groups of lymphocytes and polymorphonuclear leucocytes. Here and there multinucleated giant cells were found. A few eosinophil myelocytes were seen.

Section from the left femur showed more advanced changes. The cancellous bone had been replaced by granulomatous tissue similar to that found in the ribs and skull but occasional areas of frank necrosis were present. These necrotic zones were surrounded by

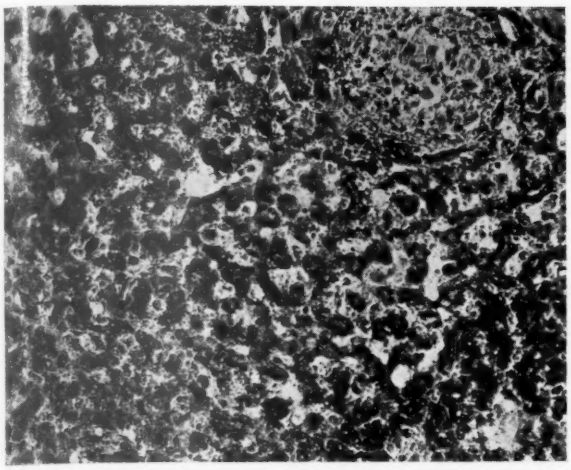

FIG. 5.—Fat droplets in parenchymal cells of liver showing fatty degeneration. The granulomatous lesion is free from lipoid. Scharlach red. × 100.

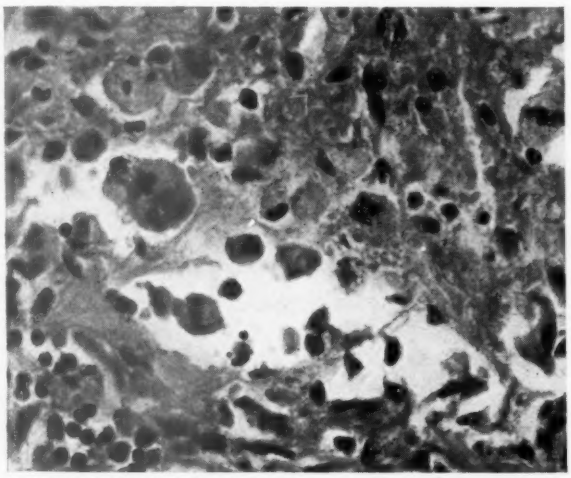

FIG. 6.—Margin of granuloma in thymus showing multinucleated giant cells. Haematoxylin and eosin. × 400.

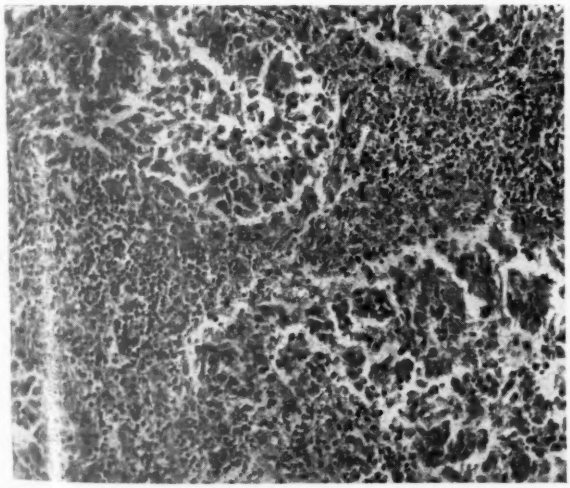

FIG. 7.—Large discrete granulomas in lymph node. Haematoxylin and eosin. × 100.

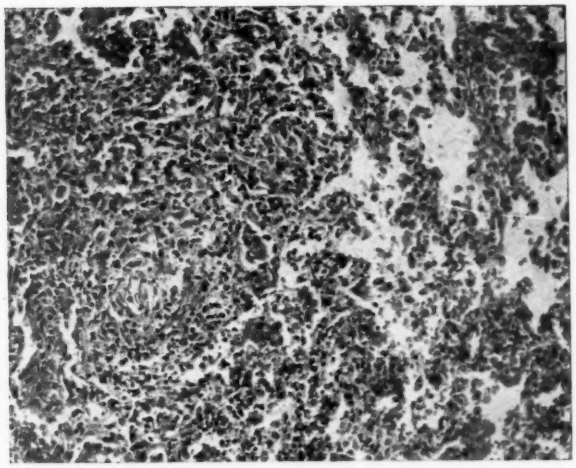

FIG. 8.—Granulomatous nodule undergoing fibrosis in interstitial tissue of lung. Numerous histiocytes in surrounding alveoli. Haematoxylin and eosin. × 100.

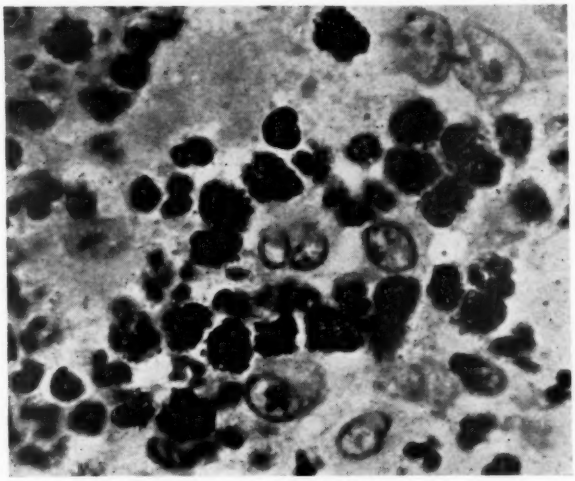

FIG. 9.—High power view of ileum to show numerous eosinophil leucocytes. Haematoxylin and eosin. × 850.

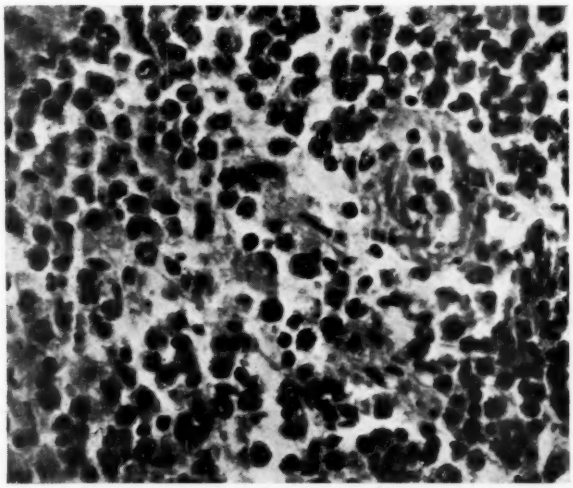

FIG. 10.—Scapula, showing eosinophilic granuloma of bone and dense collection of eosinophil leucocytes. Haematoxylin and eosin. × 400.

numerous histiocytes, giant cells, and foam cells, which were seen only close to the areas of necrosis.

The pathological diagnosis was non-lipoid reticuloendothelial granuloma: Letterer-Siwe disease.

Discussion

The first record of a similar case was made by Letterer (1924) who believed that he was dealing with 'aleukaemic reticulosis.' Between Letterer's first report and the present day some 20 cases have been recorded, the most recent being that of McKelvie and Park (1950). There also have been reported some 13 cases transitional between Letterer-Siwe disease and Hand-Schüller-Christian disease.

Siwe (1933) had regarded the disease as a non-lipoid reticuloendotheliosis of unknown origin and had described the following diagnostic criteria:

> (1) Marked splenomegaly with moderate to pronounced enlargement of the liver.
> (2) A haemorrhagic tendency, chiefly manifested as petechiae or purpura.
> (3) Generalized enlargement of lymph nodes which are discrete and not tender.
> (4) Localized defects in bones which may be detected only by radiographic examination or at necropsy.
> (5) The blood picture is that of a progressive, non-regenerative anaemia.
> (6) The disease is neither hereditary nor familial, and occurs exclusively in infants. The onset is acute and the outlook is unfavourable. The duration varies from a few weeks to a few years. The aetiology is unknown.
> (7) The characteristic pathological lesions show generalized hyperplasia of histiocytes in various organs, especially the spleen, liver, lymph nodes, thymus gland, skin, and bone marrow.

The case we have described presented these clinical features. In our patient the haemorrhagic tendency was manifested by a transient purpuric rash. There were no true cutaneous lesions of a seborrhoeic or eczematous nature. Skin lesions of a similar nature have been described in Hand-Schüller-Christian disease by Herzenberg (1928), by Lane and Smith (1939), and more recently by Curtis and Cawley (1947) in a case of eosinophilic granuloma of bone. Such lesions are frequent but not invariable accompaniments of systemic reticuloendothelial granuloma.

The pulmonary lesions are of some importance. In our case the lesions were mostly small and only the larger granulomatous areas were undergoing fibrosis. Gross and Jacox (1942) have described a case with severe pulmonary fibrosis and cyst formation.

The progressive anaemia is the result of widespread replacement of haemopoietic tissue by the granulomas.

McKelvie and Park (1950) also review briefly the pathology and the reported cases of eosinophilic granuloma of bone, and its relationship to Letterer-Siwe disease. We will therefore pass on to other theories of the mechanism of Letterer-Siwe disease, particularly those concerned with metabolism and infection.

Rowland (1928), after describing the clinical and pathological features suggested that the disease resulted from a primary disturbance of lipoid metabolism. This hypothesis was further strengthened by the work of Epstein and Lorenz (1930), who had studied the chemical nature of the deposits in Gaucher's disease, Niemann-Pick disease, and Hand-Schüller-Christian disease. The last thus came to be regarded as a disorder of the cholesterol metabolism related to Gaucher's disease and Niemann-Pick disease. This view was accepted by Sosman (1930, 1932), Chester (1930), von Gierke (1931), and Hilton and Eden (1941). Chester (1930) and Chester and Kugel (1932) thought that Hand-Schüller-Christian disease was 'a chronic non-infectious, abacterial, inflammatory granuloma due to the deposition of various lipoid substances in the involved tissues.' They called the lesion a 'lipogranuloma' and described its characteristic features. Strong (1936) questioned the existence of a definite relationship with a disorder of lipoid metabolism. Thannhauser and Magendantz (1938) were opposed to the idea of an upset in lipoid metabolism as the fundamental cause of the condition. They maintained that the deposits of cholesterol occurred as secondary changes in granulomatous lesions composed of proliferated histiocytes. Unfortunately, they classified Hand-Schüller-Christian disease as a normocholesterolaemic type of essential xanthomatosis in spite of the fact that a number of patients with this disease have had a high blood cholesterol level. Gross and Jacox (1942) in a review of the literature found 45 cases where the blood cholesterol had been estimated. In 23 cases it was over 200 mg. % so the term 'normocholesterolaemic' should not be applied to the disease. Nevertheless, these workers were able to show that the hypothesis of a primary lipoid metabolic disorder was not firmly based, and they attracted attention to the importance of the granulomatous lesions.

If the presence of granulomatous lesions largely composed of histiocytes is accepted as the fundamental lesion in Hand-Schüller-Christian disease the connexion between the latter and Letterer-Siwe disease becomes more obvious. As Wallgren (1940) remarked, the lesions tend to affect similar structures in both diseases in a similar manner. There is little difference between the skeletal lesions in the two diseases of large numbers of foam cells in biops

or necropsy specimens from patients with Hand-Schüller-Christian disease. If, however, these foam cells are not considered of fundamental importance, the two conditions may be regarded as variants of a single pathological process.

Many workers have suggested that eosinophilic granuloma of bone, Letterer-Siwe disease, and Hand-Schüller-Christian disease are variants of a common basic disorder. This view has not passed unchallenged. Siwe (1949) has discussed the features presented by the reticuloendothelioses in children. He states that ' the concept of uniformity is correct only in so far as the reticuloendothelial system is involved in all cases.' He points out that eosinophilic granuloma of bone is a localized condition confined to the skeletal system, whereas Letterer-Siwe disease is a systemic disorder. With regard to Hand-Schüller-Christian disease, he considers that the presence of foam cells is the most important feature and is not shown by the other forms to the same extent. He does not regard the presence of these cells in all organs to be essential. Siwe considers that the cases reported by Flori and Parenti (1937) and Freund and Ripps (1941) and others are atypical examples of Hand-Schüller-Christian disease and are not transitional cases between it and Letterer-Siwe disease. He is doubtful if any such cases exist. Wallgren (1940) had suggested that the nature of the lesion might depend upon its age, foam cells only being found after a considerable period of time. Siwe is unable to accept this theory and states that neither the age of the patient nor the duration of the disease process can influence the course. We are of the opinion, however, that the evidence submitted by Green and Farber (1941) and Jaffe and Lichtenstein (1944) in favour of a common basic disorder underlying these three conditions is at least as convincing as the contrary view suggested by Siwe (1949). From a pathological point of view all three conditions result from granulomatous lesions composed of histiocytes. In the acute form these histiocytes occupy the whole lesion. In eosinophilic granuloma of bone the picture tends to be dominated by eosinophil leucocytes and in Hand-Schüller-Christian disease by foam cells, but the basic lesion is similar in all three. Furthermore, skin lesions of a similar nature have now been reported in all three disorders and radiographical differentiation of the skeletal lesions in this group would not be possible. The recent reports of lymph node involvement in eosinophilic granuloma of bone would suggest that this condition is not so localized as Siwe (1949) believes.

The transitional cases present a problem of classification. It is difficult to accept Siwe's view that they are atypical examples of Hand-Schüller-Christian disease. In the case reported by Merritt and Paige (1933) the histological appearances of many of the lesions were very similar to those found in the case we have reported. Foam cells were found in the thymus and femur but early lipoid changes were present in these sites in our case also. It is difficult to believe that the two types of lesion can occur in the same patient without there being some change from one to the other.

We believe that further clinical and histological study will accentuate the similarity between these three types of reticuloendothelial granuloma. The problem will not, of course, be solved until the aetiology is completely understood.

Aetiology. The aetiology of the reticuloendothelial granulomas is still obscure. Farber (1941), Green and Farber (1942) and other recent workers in this field are inclined to take the view that the conditions are the result of an infectious agent.

Green and Farber (1942) have stated that all attempts to transmit the disease to laboratory animals have so far failed, but they also believe the condition to be infective in origin and suggest a virus as the agent.

The pathological features of the granulomatous lesions are in keeping with an underlying inflammatory condition. The lesions in the liver and lungs in our case bore a faint resemblance to those of tuberculosis, and it will be remembered that Hand (1893) thought that he was dealing with a case of atypical tuberculosis when he first described the condition which now bears his name. If we are in fact dealing with an infectious disease further work is required to identify the causal organism.

Diagnosis. Letterer-Siwe disease, the acute form, is characterized by hepatosplenomegaly, enlargement of lymph nodes, fever, severe anaemia and changes in the skull, ribs, and long bones demonstrable radiographically. Not infrequently skin lesions of a haemorrhagic, purpuric, or eczematous nature are also present. An interesting feature in our case was the early eruption of teeth. The child had two teeth when admitted to hospital at the age of 22 weeks. Wallgren (Case 1, 1940) also noted that the teeth may erupt early in this disease. His patient had three teeth at the age of 3½ months.

The disease usually appears before the age of two years and runs an acute course ending fatally in a few weeks or months. Frequently a case, such as that reported by Merritt and Paige (1933) and others, may run a subacute course for many months, and the condition in the later stage tends to resemble the lipophagic form known as Hand-Schüller-Christian disease. The blood cholesterol is usually normal, but in the case reported by van Creveld and Ter Poorten (1935) the blood cholesterol was

596 mg. %. Pulmonary lesions are common. They resemble miliary tuberculosis in the early stages and fibrosis occurs as the disease progresses. Pleurisy and pneumothorax have been known to occur. Secondary infections such as otitis media, bronchitis, and bronchopneumonia are common. Letterer-Siwe disease is not familial or hereditary.

The pathological features of the acute form are exemplified in the case we have described. In addition to the organs affected in our case similar lesions in the pancreas, suprarenal glands, pituitary gland and Peyer's patches of the small intestine have been reported by various writers. Grady and Stewart (1934) have reported the occurrence of large cystic areas in the liver. On histological examination, the lesions were composed of masses of pale-staining histiocytes with a few lymphocytes and plasma cells. In our case the lesions in the liver and lungs were well-defined while those in the spleen, lymph nodes, and thymus gland were more diffuse. Necrosis was especially pronounced in the latter. Phagocytosis of fat droplets is not a conspicuous feature of this form and foam cells were only found near areas of necrosis. Eosinophil cells were scanty and giant cells were limited to the neighbourhood of necrotic tissue.

Hand-Schüller-Christian disease, the chronic lipophagic form, occurs chiefly in children and young adults and is neither familial nor hereditary in character. Kellog (1940) found that the majority of cases occurred in the first decade. Sosman (1932) reported a case in a male aged 55 years and Hertzog *et al.* (1940) described their findings in a male aged 54 years. These cases are exceptional.

This form of reticuloendothelial granuloma is commoner than the acute type. Gross and Jacox (1942) reviewed the literature and found 84 examples of the condition, and added a case of their own. Since then 24 cases have been reported in the literature bringing the total up to 109.

The clinical features are variable. The classical triad of multiple skin lesions, diabetes insipidus, and exophthalmos was regarded as pathognomonic of the condition by Schüller (1915). Sundelius (1936) stated that skull lesions, diabetes insipidus, and exophthalmos occurred in that order of frequency; the classical triad was the next most frequent occurrence. Horsfall and Smith (1935) classified symptoms and signs according to the frequency of their appearance, and found the classical triad was most frequent. This was followed by dwarfism, gingivitis and carious teeth, pain over bony lesions, discharging ears, lymphadenopathy and the adiposo-genital syndrome. It was soon recognized that the presenting symptoms and signs would depend on the site of the granulomatous lesions. Many cases have now been reported where the classical triad was absent. Hand-Schüller-Christian disease can appear under many guises. Snapper and Parisel (1933) have reported a case which closely resembled osteitis fibrosa cystica, and Hampton (1942) one in which the outstanding clinical sign was severe jaundice. The occurrence of dystrophia adiposo-genitalis has been described in detail by Schüller (1915), Schüller and Chiari (1930), and Chester and Kugel (1930). Dwarfism was a feature noted by Rowland (1928) and Snapper and Parisel (1933).

Deafness may result from lesions in the petrous-temporal bone and mastoid processes. Dyspnoea can occur as a result of severe fibrosis, and cor pulmonale with acute right-sided failure may result.

Chester (1930) described the occurrence of xanthelasma of the eyelid in one of his patients, while Snapper and Parisel (1935) reported spontaneous fractures of both femora in a patient with multiple granulomatous lesions in the long bones.

Headaches and localized scalp tenderness are common (Imler, 1946). Freund and Ripps (1941) reported a case where great enlargement of the cervical lymph nodes gave the patient a bull-necked appearance. It is thus obvious that in the absence of the classical triad there may be some difficulty in reaching a diagnosis.

Radiological investigation is essential. The lesions in the skull, ribs, pelvis, vertebrae and long bones have the characteristic appearance common to all types of reticuloendothelial granuloma. In the skull they are more clear cut than those elsewhere (Imler, 1946).

The radiographic appearance of early chest lesions resembles that of miliary tuberculosis. In later cases fibrosis and emphysema are found. Nearly all the fatal cases have shown extensive pulmonary lesions.

Laboratory investigations should include a differential leucocyte count and estimations of the blood cholesterol. The latter is frequently normal but in a number of cases it is markedly raised. A moderate degree of eosinophilia is commonly found.

Transitional cases between Letterer-Siwe disease and Hand-Schüller-Christian disease occur from time to time. These almost invariably end fatally. The disease tends to be more acutely progressive in very young children and the outlook is unfavourable in such cases. In older children and adults the condition is more chronic and the prognosis is better. According to Sosman (1932) the mortality in Hand-Schüller-Christian disease is 30%.

The pathological features of this form are variable. If the lesions are present in the orbits and in the region of the pituitary, exophthalmos and diabetes may ensue (Schüller, 1915; Schüller and Chiari,

1930). Frequently other skeletal structures are affected. Lesions have been reported in the petrous temporal and mastoid region, in the mandible, scapula, clavicles, ribs, pelvis, vertebrae and in the long bones. Considerable attention has been paid to the location of the granulomatous deposits which could have caused diabetes insipidus. Thompson, Keegan, and Dunn (1925) reported inflammatory changes in the brain near the tuber cinereum and in the pituitary gland, while Dietrich (1913) had also found granulomatous tissues around the hypophysis. Horsfall and Smith (1935) thought that diabetes insipidus resulted from granulomatous lesions in the region of the tuber cinereum and not in the sella turcica. The most complete neuropathological report is that of Davison (1933). He found that in the case reported by Chester and Kugel (1932) the capsule of the pituitary gland was invaded by foam cells and the tuber cinereum showed areas of gliosis.

The histological features of the lesions in Hand-Schüller-Christian disease are so striking that the examination of a biopsy specimen will provide the diagnosis. The granulomas are composed of masses of histiocytes, many of which contain fat droplets and cholesterol and have assumed the appearance of foam cells. Cholesterol clefts may be found. Eosinophil leucocytes are frequently present in the more cellular areas but seldom in such great numbers as in the eosinophilic form (Fig. 9). In older lesions some scar tissue may be found.

Eosinophilic granuloma of bone is the least severe of this group of diseases. Patients rarely succumb unless some intercurrent infection supervenes. The lesions may be solitary but multiple lesions are frequently found, and are often silent and only revealed by radiographic examination following the discovery of a lesion which has given rise to symptoms. Any bone in the body may be involved except those of the hands and feet. Multiple skull lesions are common and cannot be distinguished radiographically from those of the acute or chronic lipophagic types. Lymph node involvement has been reported but is not a common occurrence.

Jaffe and Lichtenstein (1944) reviewed the literature, and their review has been extended by McKelvie and Park (1950).

The pathology of eosinophilic granuloma of bone has been described in great detail by Green and Farber (1942) and by Jaffe and Lichtenstein (1944). The histological appearance of the lesion is characteristic (Fig. 10). Masses of eosinophil leucocytes are found in granulomatous lesions composed of solid sheets of histiocytes. There has been considerable speculation concerning the part played by the eosinophil leucocytes in this condition. They are less conspicuous in the acute form or in the lipophagic form. They are usually present in the bony lesions and not in the viscera (Ackerman, 1947), but Love and Fashena (1948) have found them in large numbers in cervical lymph nodes. The production of these eosinophil leucocytes may be the response of the organism to an infectious agent or to some products of tissue destruction caused by the granulomatous lesions.

Green and Farber (1942) have suggested that in eosinophilic granuloma of bone the lesion proceeds through a lipophagic stage and thereafter reverts to normal. Engelbreth-Holm, Teilum, and Christensen (1944) also believe that various histological stages occur in the progress of the lesion towards healing. They define the stages as (1) a hyperplastic proliferative phase, (2) a granulomatous phase, (3) a xanthomatous phase, and (4) a fibrous or healing phase. There may be cases which show these transitions but they do not necessarily occur in every instance. Jaffe and Lichtenstein (1944) have described a case where the lesion apparently healed by resolution. We have also seen a case where the granuloma was undergoing fibrosis and healing without the intervention of a lipophagic phase.

Treatment. Letterer-Siwe disease is almost invariably fatal and no treatment has any influence on the outcome. It is possible that x-ray therapy would have some effect on the subacute or transitional cases but no reports of this are available. Blood transfusions, as was found in our case, are merely palliative measures and have little effect on the final outcome.

Treatment of Hand-Schüller-Christian disease can cause a remarkable improvement both in the general health of the patient and in the repair of the lesions. Sosman (1932) has suggested a high protein, low fat, high carbohydrate diet, and recommends the use of 10 units of soluble insulin daily to promote an appetite. The patients under this regime gain weight and show an improvement in general well-being. Patients with polyuria improve after injections of pitressin, but Sosman (1932) has had even better results with x-ray therapy. He believes that the latter not only has a good effect on the bone lesions but is equally effective in controlling the diabetes insipidus. All workers agree that there is a rapid symptomatic response to deep x-ray therapy. The skeletal lesions repair more slowly in adults than in children (Sosman, 1932; Hilton, and Eden, 1941). The exophthalmos is refractory to radiotherapy. The pulmonary lesions have to be treated with care. If they are in the early miliary stage therapy may aid resolution. If, however, fibrosis has already occurred this may be increased by x-ray therapy. In cases where diabetes insipidus is a prominent

feature, little benefit can result from radiotherapy if the granulomatous lesions in the region of the pituitary have already undergone fibrosis. Imler (1946) recommends a total dosage of 600 r measured in air to the pituitary and 400 r to the bones.

Hand-Schüller-Christian disease, unlike Letterer-Siwe disease, is subject to spontaneous remissions. Such remissions have been noted both in the skeletal and pulmonary lesions (Imler, 1946).

Like Hand-Schüller-Christian disease the lesions in eosinophilic granuloma of bone may undergo spontaneous resolution. Solitary lesions respond well to surgical curettage (Hill, 1949) and both solitary and multiple lesions respond well to radiotherapy. The latter, with or without surgical curettage, is the treatment of choice in eosinophilic granuloma of bone. It is especially useful in preventing pathological fractures which are a danger if the lesions are allowed to remain untreated.

Summary

A case of Letterer-Siwe disease is presented and the clinical and pathological features are described.

The relationship between Letterer-Siwe disease, Hand-Schüller-Christian disease and eosinophilic granuloma of bone is discussed and it is suggested that these three conditions are all examples of reticuloendothelial granuloma. Letterer-Siwe disease is the most severe and fatal form and the prognosis is uniformly bad. Eosinophilic granuloma of bone is the mildest type and frequently occurs as a single lesion. Hand-Schüller-Christian disease occupies an intermediate position, and the outlook is better than in Letterer-Siwe disease, but less favourable than in eosinophilic granuloma of bone.

We wish to thank Dr. Douglas Nicholson of the Royal Edinburgh Hospital for Sick Children for permission to publish this case, and we are indebted to Professor R. W. B. Ellis for his advice and criticism.

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LETTERER-SIWE'S SYNDROME: REPORT OF A CASE WITH UNUSUAL PERIPHERAL BLOOD CHANGES

BY

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(RECEIVED FOR PUBLICATION, DECEMBER 20, 1949)

In 1933 Siwe laid down the criteria of the syndrome now called Letterer-Siwe disease, and in the literature before and after that date the different features are discussed and related to the reported cases. The following case illustrates in particular the peripheral blood changes which may occur in this condition, and a table is appended summarizing the clinical and pathological features of 18 cases beginning with Letterer's (1924) case and bringing the series up to date (1950) with the present case.

Case Report

A boy aged 3½ years was admitted on March 11, 1948, with a history of soreness of the right ankle, anorexia, insomnia, and screaming in the night. The temperature was normal. The child was very pale and had puffy eyes. Firm and discrete nodes approximately 0·75 cm. in diameter were palpable in the neck, especially in the posterior triangle, the axillae, and the groins. The tip of the spleen was easily palpable but there was some doubt about the liver being palpable. The right ankle was swollen but there was no tenderness and the movements were neither limited nor painful.

A radiograph of the chest showed a doubtful hilar shadow; the skull, humeri, pelvis, femora, tibiae and fibulae were normal.

Blood Count:

Haemoglobin, 44% (Haldane).

R.B.C., 2,300,000 per c.mm. W.B.C., 7,000 per c.mm.

Differential white count: neutrophil polymorphs, 4% (280 per c.mm.), lymphocytes, 95% (6,650 per c.mm.), haemohistiocytes, 1% (70 per c.mm.).

A tentative diagnosis of aleukaemic lymphatic leukaemia was made. During the next fortnight the temperature ranged from 90°-100° F. and a mass became palpable in the left iliac fossa.

28.3.48. Sternal puncture was performed. In the marrow films haemohistiocytes dominated the picture. Very few mature lymphocytes, granulocytes, and normoblasts were to be seen.

29.3.48. Intramuscular penicillin (20,000 units four-hourly) was started.

Wassermann reaction + +; Kahn reaction, strong positive.

Volmer patch test negative after 48 hours.

Total serum protein	5·55 g. %.
Albumin	3·83 g. %.
Globulin	1·72 g. %.
Albumin/globulin ratio	2·2:1.

The father's and mother's Wassermann and Kahn reactions were negative.

Transfusion of 1 pint of packed cells.

6.4.48. Wassermann + +; Kahn, strong positive.

7.4.48. Penicillin dosage increased to 50,000 units four-hourly.

11.4.48. Wassermann and Kahn tests negative.

Paul Bunnell test negative.

22.4.48. Penicillin discontinued.

20.5.48. X-ray examination of the humeri, pelvis, femora, tibiae, and fibulae showed no abnormality.

26.5.48. Transfusion of 1 pint of blood. The spleen was easily palpable but not the liver, owing to guarding in the right hypochondrium. By percussion the liver was found to be enlarged two fingerbreadths below the costal margin.

17.6.48. Biopsy of a lymph node from the posterior triangle.

18.6.48. Liver palpable now.

19.6.48. Child vomited a few ounces of bright blood.

20.6.48. Occult blood in the stools. Transfusion of 1 pint of packed cells. Patient now running a hectic temperature.

24.6.48. Report on section of the lymph gland diagnosed reticulum cell medullary reticulosis.

30.6.48. Haemoglobin level falling rapidly.

4.7.48. Pallor now very marked, and ulcerative angina well established. The spleen and liver were larger than before.

9.7.48. Haemorrhagic gingivitis.

11.7.48. Patient died.

The clinical features of this and other reported cases are summarized in Table 1.

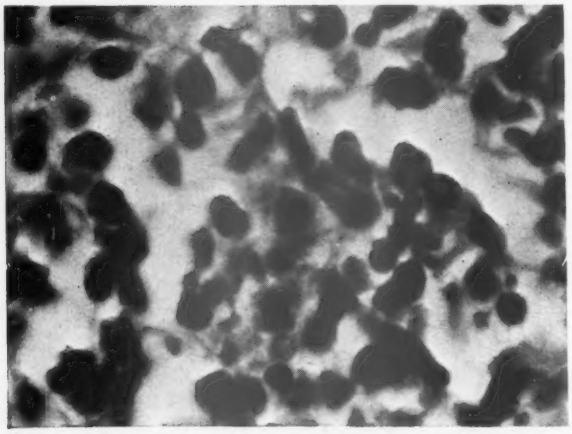

FIG. 1.—Bone marrow showing almost complete replacement by reticulum cells. Haematoxylin and eosin. × 675.

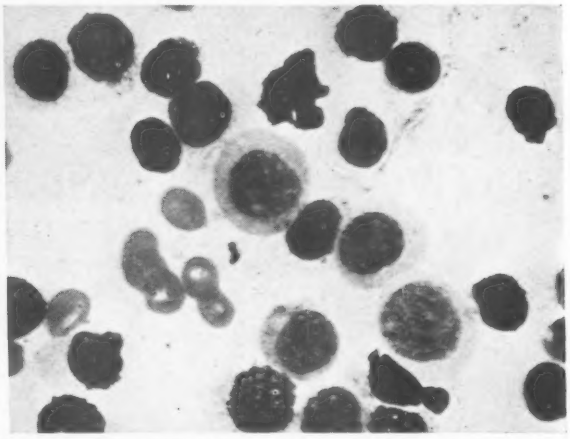

FIG. 4.—Smear of a lymph node showing large numbers of reticulum cells which are identical with the haemohistiocytes seen in Fig. 2. Leishman. × 675.

FIG. 2.—Peripheral blood smear showing binucleate form of haemohistiocyte which was present in appreciable numbers. Leishman. × 1200.

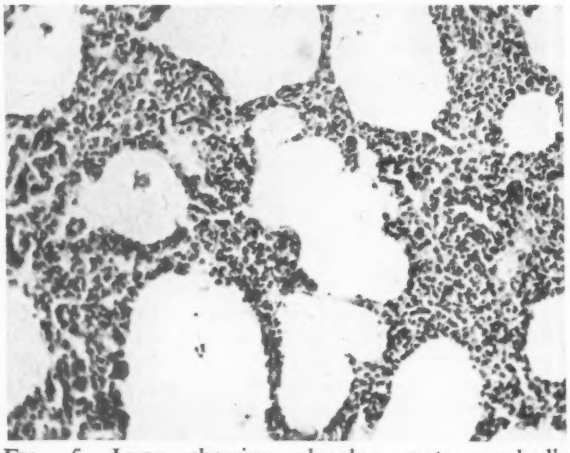

FIG. 5.—Lung showing alveolar septa markedly thickened and infiltrated by reticulum cells. Haematoxylin and eosin. × 100.

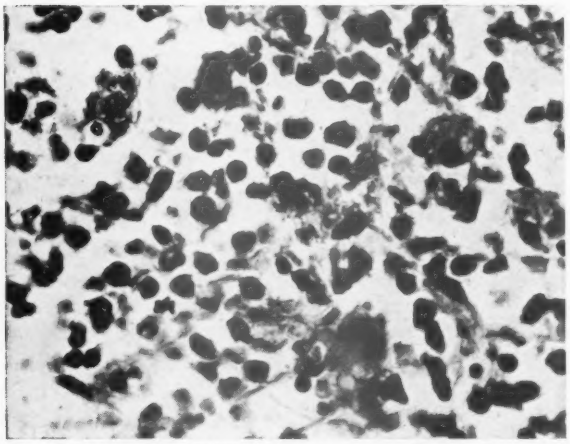

FIG. 3.—Lymph node: large numbers of reticulum cells are to be seen in the medulla. Haematoxylin and eosin. × 420.

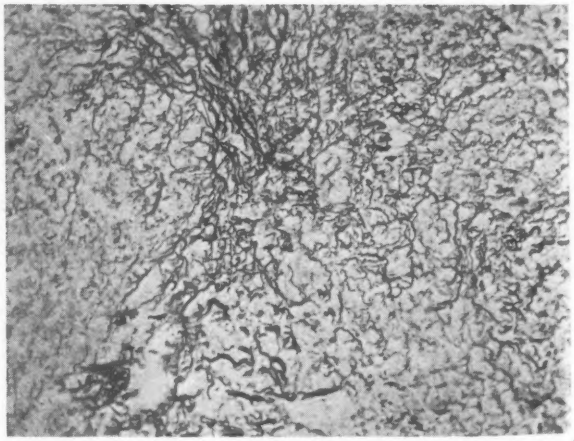

FIG. 6.—Lymph gland showing abundant formation of reticulin. Stained for reticulin. × 100.

TABLE 1

SUMMARY OF BLOOD FINDINGS IN PRESENT CASE

Date	R.B.C. (millions per c.mm.)	Hb. (Haldane) (%)	W.B.C. (millions per c.mm.)	Differential White Count					
				Neutrophil	Eosinophil	Basophil	Lymphocyte	Monocyte	Haemo-histiocyte *
March 11, 1948	2·3	44	7,000	280	—	—	6,650	—	70
,, 14, ,,	1·6	40	3,500	70	35	—	3,080	—	315
,, 21, ,,	1·6	38	3,900	195	—	—	3,042	—	663
,, 29, ,,	Transfusion of one pint of packed cells								
April 1, ,,	3·5	68	4,000	360	40	—	3,520	—	80
,, 11, ,,	3·5	68	5,400	864	—	—	4,104	—	432
,, 18, ,,	2·5	48	5,800	116	—	—	4,698	—	986
,, 28, ,,	3·0	64	4,200	84	—	—	3,528	84	504
May 16, ,,	2·3	50	6,500	130	65	—	4,875	65	1,365
,, 21, ,,	2·2	50	5,200	104	104	—	3,692	156	1,144
,, 26, ,,	Transfusion of one pint of blood								
June 9, ,,	3·2	62	6,300	252	—	—	4,158	—	1,890
,, 18, ,,	2·4	46	3,100	124	—	—	2,325	—	651
,, 20, ,,	Transfusion of one pint of packed cells								
,, 25, ,,	3·2	62	3,400	102	—	—	2,720	—	578

* The primitive cells in the peripheral blood were classed as haemohistiocytes. They were 15-25μ in diameter, having a large round reticular nucleus, a number containing nucleoli. The cytoplasm was abundant and of a pale dirty blue colour (Leishman stain). Some cells had cytoplasmic vacuoles and others fixed pseudopodia.

Post-mortem Report

External Appearance. A very pale and emaciated male child. The oral cavity showed ulcerative angina and gingivitis.

Chest. Oesophagus. Nil.

Thymus. Small and macroscopically normal.

Pleura. Left pleural sac contained one pint of yellow fluid.

Larynx. Nil.

Lung. Trachea and bronchi normal. Lungs pale: superficial area of collapse right lower lobe.

Pericardium. Nil.

Heart. Sub-pericardial haemorrhages near the apex and in the auricles.

Valves. Nil.

Vessels. Nil.

Abdomen. Peritoneum. Nil.

Stomach. Mucosa very pale.

Duodenum. Nil.

Bile ducts. Patent.

Intestines. Peyer's patches not enlarged; solitary lymph follicles of the colon were prominent.

Lymph Nodes. The cervical, axillary, pancreatico-splenic, external iliac and inguinal glands were red and varied in size from 0·75-1 cm. in diameter.

Spleen. Weight, 100 g. Cut surface dark red and firm.

Liver. Weight, 500 g. Dark terracotta colour. Structure appeared normal.

Pancreas. Nil.

Kidneys. Weight, 20 oz. Capsules stripped easily leaving a smooth surface. The cut surface was very pale.

Genito-Urinary Tract. Nil.

Brain. Very pale and macroscopically normal.

Spinal Cord. Not examined.

The sternal, vertebral, and femoral marrow was of a greyish pink colour.

Discussion

This is a case of reticulum cell medullary reticulosis with peripheral blood changes. The white blood count fluctuated between a low normal and frank leucopenia, with the lymphocyte as the predominant cell; a fair number of haemohistiocytes were invariably present. The reticulum cells showed unmistakable differentiation in two directions, namely, haemic and histiocytic. Without a doubt the haemohistiocytes in the peripheral blood and in the marrow were similar to the proliferating reticulum cells in the lymph glands, spleen, liver, lungs, and kidney. They were medullary reticulum cells with a tendency, as far as the nuclear structure was concerned, towards haemic differentiation. Definite evidence of differentiation towards histiocytes was to be seen in the liver, spleen, lungs, kidney, and, to a lesser extent, in the lymph nodes. Apart from a few departures from the accepted picture of the Letterer-Siwe syndrome (namely, the presence of haemohistiocytes in the peripheral blood, and the absence of purpura and osseous changes) the case reported satisfies the criteria laid down by Siwe. The Wassermann and Kahn reactions were strongly positive on two occasions but negative on the third. This no doubt was due to the change in the plasma globulin.

Summary

An unusual case of reticulum cell medullary reticulosis displaying the features of the Letterer-Siwe syndrome is described. A tabular review of the cases reported in the literature is presented in the Appendix.

My thanks are due to Dr. B. Barling for permission to publish the case, and to Dr. A. H. T. Robb-Smith for his helpful criticism and encouragement.

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APPENDIX

ANALYSIS OF FEATURES OF REPORTED AND PRESENT CASES

Author	Age of Patient	Presenting Signs	Duration	Clinical Features									Reticulosis of Organs				
				Pyrexia	Agranulocytic angina	Haemorrhagic Diathesis	Anaemia	Change in Blood Picture	Generalized lymph-adenopathy	Splenomegaly	Hepatomegaly	Osseous Changes	Lymph nodes	Bone marrow	Spleen	Liver	Lungs
Letterer (1924) ..	6 mths.	Purpura sepsis	11 wks.	+	−	+	−	+	+	++	+	None clinically	++	+	++	+	?
Akiba (1926) ..	10 mths.	Purpura sepsis	6 wks.	+	+	+	+	?	+	++	+	„ „	++	?	++	+	−
Krahn (1926) ..	5 years	Sepsis	6 mths.	+	−	+	+	S	+	++	−	„ „	++	++	++	++	?
Sherman (1929) ..	11 days	Jaundice erysipelas	4 days	+	−	−	+	−	−	+	+	„ „	?	+	+	+	++
Guizetti (1931) ..	3 mths.	Cough, fever, epistaxis	21 days	+	−	+	+	−	?	++	++	Cystic changes in the right humerus on x-ray examination	++	++	++	++	+
Podvinec and Terplan (1931)	1 year	Fever	14 days	+	+	+	−	−	+	++	++	None clinically	++	++	++	+	+
Uher (1933) ..	1¾ years	Sore throat, fever	17 days	+	+	+	−	S	+	+	+	„ „	++	+	++	+	++
Siwe (1933) ..	16 mths.	Swelling of the left leg	4 mths.	+	−	+	−	S	+	+	+	Cystic changes in the left fibula on x-ray examination	+	++	++	++	−
Gittins (1933) (*a*)	23 mths.	Anaemia	24 mths.	+	−	++	++	S	−	+	+	None clinically	++	++	++	+	?
(*b*)	21 mths.	Anaemia abscesses	3 wks.	+	−	+	++	+	+	+	−	„ „	++	++	++	+	?
(*c*)	1 year	Anaemia	11 days	?	−	−	++	+	+	++	++	Slight x-ray changes	+	−	++	+	?
(*d*)	17 wks.	Anaemia	4 mths.	−	−	S	++	+	+	++	+	None clinically	+	+	++	+	+
Klostermeyer (1934)	13 mths.	Swelling of the face	7 wks.	+	+	−	+	A	+	++	++	„ „	++	+	+	+	?
Foot and Olcott (1934)	2¾ years	Purpura, otitis media	1½ years	−	−	+	−	+	−	++	++	X-ray examination revealed rarefaction of the pelvis, upper end of the right femur. Osteoporosis of the spine at first suggested Pott's disease	++	++	+	+	+
Roussy and Oberling (1934)	8 mths.	Purpura	1 mth.	+	−	+	+	S	+	++	+	None clinically	++	+	++	++	++
van Creveld and Ter Poorten (1935)	4 mths.	Otitis media	8 wks.	+	−	−	−	S	+	+	+	Cystic changes in the skull, head of the right humerus and lower end of the right femur	+	++	+	+	++
Abt and Denenholz (1936)	2 years	Tumour of the skull	4½ mths.	+	−	+	+	+	+	++	++	Pulsating tumour of the skull. On x-ray examination a cystic area was apparent	++	++	++	++	++
Present case ..	3½ years	Swelling of right ankle, anorexia, insomnia	4 mths.	+	+	S	++	A	+	+	+	None clinically	+	++	++	++	++

?=Not mentioned. S=Slight. A=agranulocytosis.

CEREBRAL ANOXIA IN INFANTILE DEHYDRATION

BY

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(RECEIVED FOR PUBLICATION, SEPTEMBER 16, 1949)

The severe constitutional symptoms appearing in the course of infantile diarrhoea form a characteristic picture referred to as toxicosis. The most prominent features of this toxic condition are medical shock, acidosis, acidotic breathing, functional failure of the kidneys and characteristic nervous symptoms. Clinically the nervous symptoms are characterized by extreme prostration, sometimes preceded by great restlessness. In severe cases there is complete loss of consciousness similar to uraemic or diabetic coma. Frequently cataleptic features are seen, such as the 'fencing position' of the extremities and fixation of the eyeballs. There are signs of disturbance of the autonomic nervous system, and the purpose of this paper is to analyse the origin of these nervous symptoms.

Originally the direct effect of dehydration on the brain was thought to have a bearing on the origin of the nervous disturbances (Bessau, 1921). The water content of the brain was, however, found to be normal.

That acidosis is not responsible for the severity of cerebral symptoms is shown by the fact that acidosis may be corrected by bicarbonate solutions while the cerebral symptoms may persist (Csapó and Wollek, 1935). On the other hand, death frequently occurs in spite of correction of the acidosis (Hartmann, 1928).

In Germany for the last two decades the theory of Bessau and Rosenbaum (1928) has been widely accepted. Dehydration was thought to increase the permeability of the 'blood-liquor barrier,' and result in endotoxins originating from coli or dysentery bacilli gaining access to the brain tissue.

Histological changes of the brain tissue have been described and have been considered to be of aetiological importance (Goldzieher, 1930; Schaferstein, Popowa, and Owtscharenko, 1935; Marquézy and Ladet, 1938; Kramár and Miskolczy, 1940; Christensen and Biering-Sörensen, 1946). The meninges were found to be injected and oedematous. In the parenchyma the dilated capillaries were encircled by oedematous, loosened brain substance. There was evidence of cellular degeneration amounting in some cases to necrosis. As leucocytic inflammatory changes have been absent, the picture has often been called encephalosis.

On the other hand, one of us (Kerpel-Fronius, 1947) reviewing evidence based on the pioneer work of Marriott (1920), Gamble (1928), and others, emphasized again that toxicosis is primarily a condition similar to medical shock. The failure of circulation may or may not be due exclusively to anhydraemia.

A fundamental feature of medical shock is the slowing of the peripheral blood flow, thus resulting in a condition of anoxia of the stagnant type. Marriott (1920) and Utheim (1920), using a calorimetric method, measured a diminished blood flow to the extremities per unit of time in infantile toxicosis. Thus it is to be expected that the blood supply to the brain may also be diminished. We have attempted to verify this assumption. If the blood supply to the brain be diminished, the oxygen saturation of the venous blood leaving the brain should decrease. The extent of this anoxia, if a consequence of medical shock, should be related to the extent of the slowing of the blood flow. Finally it remained to be seen whether the expected anoxia had or had not a bearing on the origin of the nervous symptoms. For this purpose oxygen saturations of the cerebral blood were determined in clinical cases varying from mild dehydration to deep coma, the degree of anoxia being compared with the severity of the nervous symptoms.

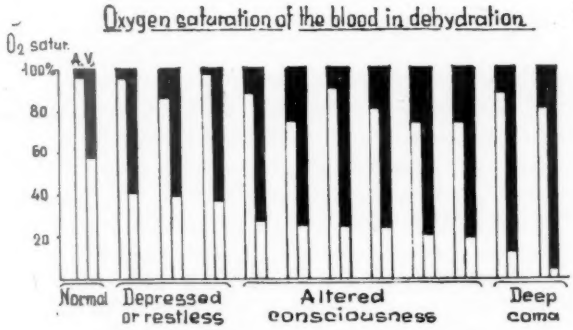
Methods

Arterial blood was drawn under oil from one of the arteries of the head or arm. Venous cerebral blood was taken from the longitudinal sinus. The oxygen content of the blood was determined by Van Slyke's method. Circulation time was measured by injecting Congo red dye into the left cubital vein, another needle being simultaneously inserted into the right cubital vein. At intervals of exactly three seconds blood was withdrawn into heparinated glass capillaries. After the separation of the plasma from the corpuscles, the first appearance

of the dye was clearly visible. The time elapsing from the injection to the first appearance of the dye in the vein of the corresponding arm is the circulation time.

Results

Fig. 1 shows the oxygen saturation in the arterial and cerebral venous sinus blood of 11 dehydrated infants.



A=arterial oxygen saturation V=venous oxygen saturation.

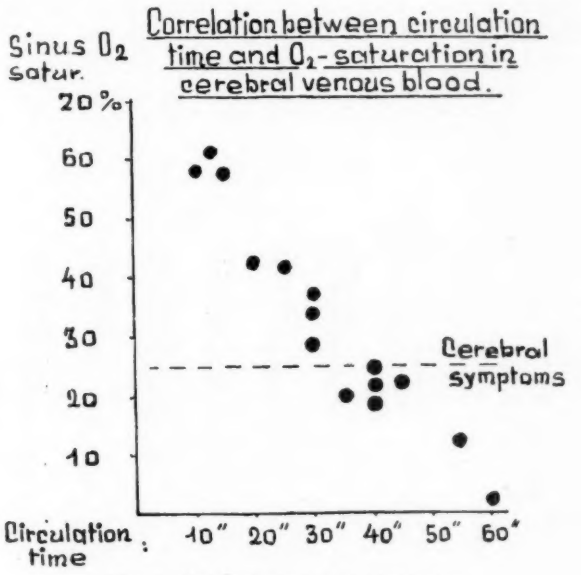
FIG. 1.—Diagram showing oxygen saturation in the arterial and cerebral venous (sinus) blood of 11 dehydrated infants and one normal.

Each column represents an individual case. Reading the figure from left to right, cases are progressively more severe. The figure shows that parallel to the increasing gravity of the clinical condition, the arteriovenous oxygen difference is progressively greater. That is a proof of slowed cerebral circulation.

It is also seen that the oxygen saturation of the blood of the longitudinal sinus is becoming progressively less in cases of increasing severity. The cerebral symptoms characteristic of the toxic phase of dehydration appeared when the oxygen saturation of the cerebral venous blood approached 25%. Deep coma was observed when the latter decreased to less than 15%.

In a number of cases arterial oxygen saturation is also somewhat lowered. That is probably due to paravertebral pulmonary congestion. Low arterial oxygen saturation is obviously disadvantageous when superimposed on anoxia of the stagnant type. It is thus comprehensible that in infantile dehydration intercurrent pneumonia greatly facilitates the appearance of toxic symptoms.

Fig. 2 shows the circulation times plotted against cerebral venous oxygen saturations. The close correlation between decreased oxygen saturation in the cerebral venous blood and medical shock as measured by circulation time is clearly visible. The longer the circulation time, the severer the cerebral anoxia. The cerebral symptoms characteristic of toxicosis appeared at an approximately trebled circulation time of about 40 seconds; at this point we invariably found oxygen saturations below 25%.



●=individual case of dehydration.

FIG. 2.—Diagram of circulation times plotted against cerebral venous oxygen saturations

Discussion

Our data reveal that the cerebral symptoms in infantile toxicosis appear when the degree of venous anoxia reaches a certain point. That this anoxia is of aetiological importance in the genesis of the comatose condition can be confirmed by the following data. In anoxia due to a slowed circulation each portion of blood gives up a larger proportion of its oxygen load in the proximal capillaries. Consequently in the more distal capillaries a large part of the oxygen is delivered under low pressure. As oxygenation is a function of pressure, a large part of the brain will receive insufficient amounts of oxygen. In this respect the work of Lennox, Gibbs, and Gibbs (1935) is of great interest. These authors studied the relation of unconsciousness to the supply of oxygen in normal adults, inducing lack of oxygen by breathing nitrogen or by experimental syncope. Unconsciousness resulted in every case when the oxygen saturation of the blood from the internal jugular vein was less than 30%. It may be seen that this figure closely corresponds to our figures as found in the blood of the longitudinal sinus in toxicosis. Fig. 3 gives additional data, and shows that in infantile bronchopneumonia, where the anoxia is chiefly arterial, unconsciousness results when about the same degree of cerebral anoxia is reached as in toxicosis or in artificial syncope. The construction of Fig. 3 corresponds to that of Fig. 1.

It may be seen from our six cases of infantile

bronchopneumonia that the arteriovenous oxygen difference is generally normal; thus, in contrast to toxicosis, the velocity of cerebral blood flow is unchanged. The arterial oxygen saturation due to insufficient oxygenation in the lung is, however, so

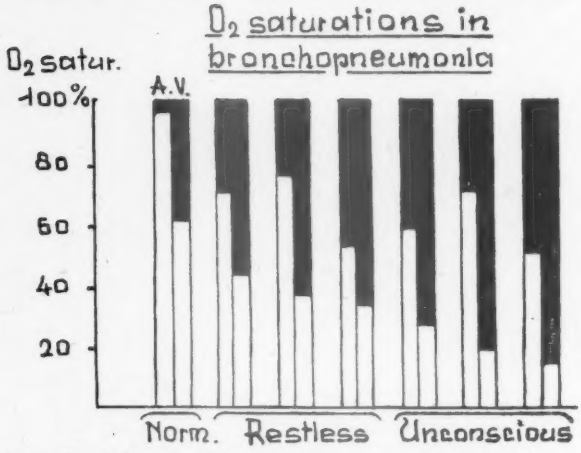


FIG. 3.—Diagram illustrating oxygen saturation in six cases of bronchopneumonia and one normal.

low that in severe cases the oxygen saturation of the blood of the longitudinal sinus is as low as in toxicosis. In the latter case, bronchopneumonia was accompanied by unconsciousness.

Coma, probably due to lack of oxygen, may in certain conditions be of a more complicated origin and can be revealed only by measuring the oxygen consumption of the brain. Kety *et al.* (1948) have found that in diabetic acidosis coma was associated with, and probably the result of, a 40% reduction in cerebral utilization of oxygen which occurred in spite of a generally augmented cerebral blood flow and normal oxygen saturation. Thus coma seems to result both in diabetes and toxicosis from the same mechanism, namely, the lack of oxygen. The latter is brought about in toxicosis chiefly by simple slowing of circulation, i.e. by shock, while in diabetes more complicated factors are operating. Last, it should be remembered that the cerebral signs of toxicosis have some features in common with the picture of lack of oxygen as observed in studies of aviation medicine.

The very low oxygen saturation in cerebral venous blood may have a bearing on the origin of some of the histological changes described in the brain of dehydrated subjects. Henry, Goodman, and Meehan (1947) studying arm veins of adults, found that in conditions in which the venous oxygen saturation falls below a critical level of 25 to 15%, a significant increase in permeability to protein occurs. The pericapillary oedema in the brain of toxic infants may thus be a sequel of anoxia.

Summary and Conclusions

The oxygen saturation of the blood of the longitudinal sinus was determined in 11 dehydrated infants. The oxygen saturation decreased parallel to the gravity of the clinical condition. A close correlation was found between the decrease of the oxygen saturation of the cerebral venous blood and anhydraemic shock as measured by circulation time. The longer the latter, the lower the oxygen saturation of the former. The cerebral symptoms characteristic of a toxic condition in dehydration appeared when the oxygen saturation of the cerebral venous blood approached 25%. Deep coma was observed when the latter decreased to less than 15%. Thus, the cerebral symptoms of severe dehydration appear to be due to cerebral anoxia of the stagnating type.

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SCURVY AND TUBERCULOUS PERITONITIS

BY

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(Received for Publication, October 2, 1949)

Frank scurvy occurring in the later years of childhood has always been so uncommon that references in the literature are few. In 1894 Sutherland listed 71 cases: of these, only 14 were over the age of two years and only five were over the age of five years. In the United States scurvy in childhood (as distinct from infancy) has been termed 'a distinct rarity' (McIntosh). A case is, however, reported of a boy of seven years (Hartman and Friedman, 1931) who had been brought up on a diet containing little vitamin C.

The following case of scurvy, first diagnosed at the age of 10 years and 11 months, is interesting, first because there was a previous history of tuberculous peritonitis associated with prolonged diarrhoea, and secondly because the child had exhibited dietetic habits of such perverseness that they might have been directed to the entire exclusion of ascorbic acid.

Case Report

Dorothy H. (born February 5, 1938) was brought to the Out-patient Department of Alder Hey Children's Hospital, Liverpool, in December, 1948, with a limp. Intermittently during the previous 12 months she had complained of nocturnal pains in her legs, which had been sufficiently severe to make her cry. She had also had a sore mouth on many occasions since early childhood, and, during the preceding five weeks, her gums had shown a tendency to bleed.

Past illnesses included measles, whooping cough, and chickenpox. At the age of 5½ years (in September, 1943) the child had been taken to another hospital with a history of loose stools during the preceding three months and loss of weight. A diagnosis of tuberculous peritonitis was subsequently made and the child was in hospital for six months under the care of the late Dr. William Johnson. While in hospital the abdomen was described at first as 'doughy,' and later was distended (circumference 22½ in.). The child was afterwards observed as an out-patient until December, 1945, and her general condition was noted to be good, although her stools were once reported to be watery, and it was recorded at one time that she had a limp. There is no further medical record until she came to Alder Hey Hospital in December, 1948.

The child was found to be small for her age, her weight being 48 lb. and height 49 in. Examination of her mouth revealed petechiae on the hard palate, and the teeth were seen to be deeply pitted. There was oral foetor and the appearance of the gums was striking: they were deep purple in colour, swollen and fleshy, and they bled easily on palpation. A petechial rash was also noted on the buttocks, extensor aspects of the elbows, and dorsa of the feet. There was follicular hyperkeratosis over the anterior aspects of the legs. The right knee was slightly swollen and was tender over the inner aspect. Attempts at passive movement of this joint were resisted as, also, was rotation of the right hip joint.

Enquiry into the dietetic history revealed that the child would eat neither fruit nor green vegetables. She liked cooked meats but not potatoes, nor butter, and she would not drink milk. Her staple diet consisted of bread and margarine and her favourite beverage was tea with a very little milk. She consistently avoided milk and meals at school and would not visit the houses of friends unless special dishes were prepared for her. The perverseness of her appetite caused comment everywhere and her mother laboured continually to obtain the few things that she would eat. She had always been underweight, even in infancy. She had not been breast-fed and feeding had always been a problem. At the age of three years she was evacuated to Shropshire and there her diet had included a considerable amount of fruit, to which she had shown marked sensitivity with skin reactions.

The child was admitted to Alder Hey Children's Hospital on December 30, 1948, for an initial period of observation and for biochemical and x-ray investigation.

Blood Chemistry. On the day of admission the plasma ascorbic acid was 0·3 mg. % and the blood haemoglobin 92% (Haldane). The mean daily urinary ascorbic acid excretion was 4·3 mg. The capillary fragility, platelet count, bleeding, clotting and prothrombin times were all within normal limits. During this initial period of observation, lasting six days, the child received and took the ordinary ward diet. An ascorbic acid saturation test was then started, giving a daily test dose calculated at the rate of 70 mg. of ascorbic acid per stone of body weight. Specimens of urine were collected over a 2¼-hour period, beginning four hours after the test dose. Low values (0·8 to 3·0 mg.) were obtained for the first five days, the figures then rising sharply on the sixth, seventh, and eighth days to 8·5 mg., 15·0 mg. and 36·0 mg. respectively. The serum calcium, inorganic phosphorus, and protein levels were estimated at the completion of the test

and were all within normal limits. The serum alkaline phosphatase level was 20 King-Armstrong units.

Radiological Report. Radiographs of the long bones showed marked thinning of the cortex, and white lines of Fraenkel were especially prominent in the region of the knee joint (Fig. 1). Trabecular markings were fairly clear

FIG. 1.—Radiograph of the long bones.

but the distal portions of the metaphyses showed some rarefaction and there were lateral spurs in the periosteum of the lower femoral diaphysis. Some swelling of the soft parts was also evident in the knee joints.

Dental Report. The gingivae were inflamed, painful and spongy, the papillae were haemorrhagic and grossly hypertrophied, and there was marked swelling over the site of the erupting second molars. The enamel of the incisor teeth was severely pitted from tip to the cervical margin and, on the facial aspect, showed some deficiency (Fig. 2). The periodontal membrane and alveolar bone seemed to have escaped gross disease because there was no loosening of the teeth.

Psychiatric Report. The child was of a gentle, reserved nature, lacking in self-confidence, anxious to please, but listless and hesitant in her responses. Her intelligence was estimated at 78 (revised Stanford Binet scale). The psychiatrist was of the opinion that the defective appetite had been present since birth: lack of breast feeding and early separation from the mother were thought to have some bearing on this. A great deal had been made of the child's poor appetite by her family and others, and she had consequently been the centre of attention. This appeared to have delayed her emotional development and made her unduly dependent upon her mother.

The conclusion was reached that during the past 18 months the deficiency in the child's diet had undermined her physical and mental energies to the extent that both intellectual and school progress had been hindered.

Treatment and Progress. After admission to hospital little difficulty was encountered in feeding the child. She ate the same meals as the other girls in the ward and readily relinquished her previous dietetic fads.

After the saturation test had been completed a dose of 25 mg. of ascorbic acid was given twice daily in addition to the normal ward diet: she received no other added vitamins.

There was a rapid improvement in her oral condition; the gums became firm and decreased in size, and the foetor disappeared. She gained 10 lb. in weight and 1 in. in height in two months. Concurrently with this physical improvement, her mental state showed a good response; she became more alert, cooperative, and interested in her companions. Her mental age advanced to 10 years and her intelligence quotient to 90. She was no longer tired and never complained of pains in her limbs. The limp, however, proved more persistent, but physiotherapy with massage, active movements, and re-education enabled her to overcome this disability by the time she was discharged from hospital on February 24, 1949.

The child has been observed as an out-patient for six months since discharge. At the end of this time she was still improving mentally and, physically, was making good progress. She was still eating a normal diet, including fruit and green vegetables. She also continued to take 50 mg. of ascorbic acid daily.

Discussion

Interesting aspects of this case include the previous history of diarrhoea and tuberculous peritonitis, the unusual age at which gross manifestations of scurvy

FIG. 2.—Photograph showing pitting of the enamel of the teeth.

became evident, the considerable physical retardation and emotional immaturity and the gratifying response to treatment.

It is difficult to ascertain for how long this child

had suffered from a lack of vitamin C. The feeding difficulty was said to date from soon after birth. The radiological and dental pictures suggest chronicity and it had been noted, when the child was convalescing from tuberculous peritonitis, that she had a limp. It might be surmised either that a lack of vitamin C predisposed the child to tuberculosis, or that this latter condition, and the associated diarrhoea, precipitated the scurvy.

Many writers have considered the probability of a mutual relationship between scurvy and infections in general and tuberculosis in particular. The relationship between diarrhoea and vitamin C lack has also been extensively studied.

Russell, Read, and Rouse (1944) found that scurvy led to extensive tuberculous lesions and widespread dissemination in experimentally infected guinea-pigs. Similar results had been obtained by Clausen (1934), Grant (1930), Greene, Steiner, and Kramer (1936), Steinbach and Klein (1941). Abbasy, Harris, and Ellman (1937) found that in patients with pulmonary tuberculosis there was a 'deficit in vitamin C' as shown by a lowered urinary excretion of the vitamin and a diminished response to a test dose; Abbasy, Gray Hill, and Harris (1936) also showed a low rate of excretion of vitamin C (an average of 9 mg. a day) in 23 cases of active surgical tuberculosis. Höjer (1924), in an extensive treatise, considered the two possibilities: the influence of tuberculosis on scurvy, and the influence of scurvy on tuberculosis. With regard to the former possibility he quotes Hess (1920): 'Active tuberculosis is a not uncommon secondary manifestation' of scurvy. Höjer also points out that in tuberculosis there may be decreased appetite and the condition of the intestinal wall may become altered so that 'the consumed dose of antiscorbutic is prevented from having an effect.' On the other hand Höjer recorded that his observations 'lend countenance to the notion that the resistance of the body to tuberculosis is lessened during the course of scurvy.'

The antecedent history of diarrhoea is also likely to be relevant in this case. Hess and others drew attention to the occurrence of scurvy following dysentery during the 1914-1918 war. As early as 1892 Northrup reported a case of scurvy in a child aged three years suffering from diarrhoea. Abt and Farmer (1941) reported on three infants during the course of non-specific diarrhoea; they noted low plasma values and low urinary levels but an increase in faecal excretion of ascorbic acid when large amounts were given by mouth. Aron (1928) observed that scurvy might occur both in the infant and in the older child following dysentery or diarrhoeal diseases. Meyer and Robinson (1939) reported low levels of vitamin C in plasma and urine in infants suffering from diarrhoea in Palestine. (Several of the children in this series had bacillary dysentery.)

In the absence of vitamin C assessment at an earlier age, it does not seem possible, in this case, to decide whether the scorbutic tendency preceded the diarrhoea and tuberculous peritonitis, or whether these conditions precipitated the scurvy. As Abt and Farmer have said 'diarrhoeal disturbance may initiate scurvy' and that may have been true of this case.

Summary

A case of scurvy is described in a girl of nearly 11 years. Her previous history included tuberculous peritonitis, and this may have had a relationship to the development of scurvy which was chronic in nature and was accompanied by physical and mental retardation. The aetiology is discussed and the result of treatment described.

I wish to thank Professor N. B. Capon for his most helpful criticism and advice, Dr. E. G. Hall for his willing cooperation and valuable comment on the pathological aspects, Dr. M. Barton Hall for the psychiatric opinion, Dr. W. Holden and Dr. J. A. Ross for radiological observations, and Professor H. H. Stones and Mr. K. Richards for the dental report.

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HYPERTROPHY OF THE LOWER LIMBS WITH CUTANEOUS NAEVUS AND VARICOSE VEINS

BY

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(Received for Publication, July 22, 1949)

The occasional occurrence of hypertrophy of a limb associated with cutaneous naevi or haemangiomata, together with congenital or developmental defects of the arteries and veins, has long been recognized.

In 1858 Adams described a 'singular case of Hypertrophy of the Right Lower Extremity with Superficial Cutaneous Naevus of the Same Side.' This appears to be the first description of such a condition in English.

Trélat and Monod (1869) in their treatise on unilateral hypertrophies of the limbs, recognized the association of hypertrophy of the bones of one leg with cutaneous naevi and varicosities of the veins of the affected limb. The limitation of the vascular anomalies to the abnormally long limb led them to believe that the two had a common developmental origin.

Under the title *Du naevus variqueux ostéohypertrophique*, Klippel and Trenaunay (1900) described a condition the main features of which were: (1) A superficial naevus of the lower limb, (2) varicosities of the veins on the same side as the naevus, (3) hypertrophy of the affected lower limb, involving the soft and bony tissues, overgrowth of the skeleton being especially prominent. It was thought possible that these anomalies had a common congenital origin.

In his classical paper, Parkes Weber (1918) described the association of congenital or developmental hypertrophy of the limbs with dilatation of the arterial and venous trunks. He collected several examples of this condition from the literature, to which the collective name of 'haemangiectatic hypertrophy' was given. This type of enlargement he differentiated from congenital trophoedema of the Nonne-Milroy-Meige type and also from that met with in simple hemihypertrophies of the limbs. In the latter, cutaneous naevi or haemangiomata are by no means uncommon, but there is no abnormality of the arteries or veins of the affected limbs.

The condition of dilatation of arteries and veins has been given the pathological appellation of 'congenital or developmental phlebarteriectasis,' of which several clinical varieties have been recognized. In the most extreme form a free anastomosis may exist between dilated arteries and veins. In a less severe form, to which the term 'genuine diffuse phlebarteriectasis' has been applied, there is no abnormal communication between the dilated arteries and veins. When the arteries are little affected, the dilatation being confined mainly to the veins, the condition is called 'genuine diffuse phlebectasis.' This last group may be considered to be one variety of congenital varicose veins in contrast to that caused by congenital obstruction in a main venous trunk. In all these types of haemangiectatic hypertrophy, cutaneous naevi or haemangiomata are commonly but not invariably present.

The condition described by Klippel and Trenaunay in which the veins alone are affected is probably best considered to be a member of the larger group of haemangiectatic hypertrophies. This syndrome appears to be closely related to, if not identical with, genuine diffuse phlebectasis or congenital varicose veins. It is interesting that in the earlier descriptions of congenital varicose veins, hypertrophy and cutaneous naevi are frequently mentioned as incidental findings (Champendal, 1900, and Besson, 1919, quoted by Lian and Alhomme, 1945).

Since the publication of Parkes Weber's paper in 1918 several examples of hypertrophy of limbs associated with vascular abnormalities have been recorded. Paterson and Wyllie (1925) described a case of hypertrophy of the bones of a limb due to a naevus. Under the title of 'haemangiectatic hypertrophy' cases have been described by Beatty (1927), Gray (1928), East (1932), Blumgart and Ernstene (1932), and Reichenheim (1943). Gougerot and Filliol (1929) described a case under the title *Naevus variqueux ostéohypertrophique de Klippel ou Hémangiectasie de Parkes Weber*. They also collected six earlier cases from the French literature.

Downing (1933) recorded a case described as *Naevus flammeus et varicosus: hemihypertrophy.* Freund (1936) collected 15 cases of diffuse genuine phlebectasia from the literature and described a further one. Examples of congenital varicose veins associated with limb enlargement have been described by Servelle (1945; 1947), Lian and Alhomme (1945). The latter give the subsidiary title of Klippel-Trenaunay syndrome to their paper. Louis-Bar and Legros (1946) described three cases of 'partial hypertrophy with angioma (Klippel-Trenaunay syndrome)'. Van Bogaert and Kegels (1947) have recorded a further case of Klippel-Trenaunay syndrome. Congenital arteriovenous communications associated with hypertrophy have been described by Reid (1925), Pemberton and Saint (1928), Lewis (1930), Horton (1934), Reid and McGuire (1938), Ward and Horton (1940).

The present case approximates to that form of haemangiectatic hypertrophy in which there is minimal abnormality of the arterial system, the main vascular defects being those of the skin and the superficial veins, the syndrome accurately defined by Klippel and Trenaunay in 1900.

Case History

The patient is a boy born on December 10, 1941. When he was seven years old he was referred to a plastic surgeon with the complaint that the right lower limb had been larger than the left since infancy and had increased in size in the past year. It was also thought that the left foot, although not so large as the right, was considerably larger than normal. Shortly afterwards he was admitted for investigation.

He is the only child, and was born at term. Delivery was normal (birth weight, 7 lb.).

At the age of 17 years his mother developed varicose veins of the right lower limb. During pregnancy, when 20 years old, varicose veins appeared on the left lower limb, and those of the right became more prominent. Since that time she has had repeated injections of sclerosing substances into the veins without much relief. The mother has no cutaneous naevi, and there is no asymmetry or enlargement of the limbs. There is no history of a similar condition in other members of the family. The parents are not blood relations.

At birth it was seen that the right lower limb was longer than the left. There was no apparent difference in girth of the lower limbs at this time. An extensive birthmark was present on the right thigh, the right side of the abdomen, and on both sides of the chest. A soft swelling was noticed on the lower part of the right anterior chest wall. A more extensive swelling of a similarly soft consistency was seen on the left side of the abdominal wall.

In the neonatal period and in early childhood his health was good. He had measles and whooping cough when he was four years of age. Mental development has been normal. He went to school when five years old and is in a class of children of his own age. Since he first wore shoes he has always had to have a larger shoe for the right foot than the left. Until he was five years old, in spite of the greater length of the right leg, he suffered no disability and there were no subjective complaints. At this time he began to have attacks of dull, aching pain in the right calf and thigh which recurred every two or three months. The pain was precipitated by over-exertion during the day, or occurred when he was warm in bed. It would last for several hours and was relieved by rest or locally applied heat. Occasionally the right lower limb felt hot and throbbed, at which time the birthmark on the thigh became a deeper colour. In the past two years the attacks of pain have become more frequent and at present occur every three of four weeks. In the past year the right lower limb has increased in girth. During this time prominent veins have appeared on the right thigh, below the right knee and on the front of the right ankle. Coincident with the attacks of pain the veins have been swollen and tender. The swellings on the chest and abdomen have not increased in size recently, but another similar swelling was noticed a year ago in the right groin. In spite of the repeated pains in the leg the patient has not been greatly incapacitated. He leads a normal life at school, is able to run and plays games.

No asymmetry or increase in size has been observed in the upper limbs. The birthmark has not become more extensive since infancy.

Clinical Examination. The patient was a thin, agile boy of good intelligence. Height, 51½ in. Weight, 71 lb. The right lower limb was appreciably larger than the left both in length and in girth, with considerable obliteration of the bony outline of the right knee. Both feet were abnormally large, the right more than the left. The second toe of the right foot was especially prominent. The increase in length of the right lower limb appeared to be equally distributed between the thigh and leg. The right buttock was enlarged. There was no scoliosis, but the right side of the pelvis was tilted upwards and there was a lumbo-dorsal lordosis. The upper limbs were of equal size. There was no asymmetry of the face or thorax. The musculature of the upper part of the body was poorly developed. The abdomen was protuberant, the left side more than the right.

An extensive naevus covered the greater part of the right lower limb, and part of the anterior abdominal wall, chest, and back. It was not raised above the skin surface and was of the naevus flammeus or 'port wine stain' variety. In colour it varied from a violet-pink on the right lower limb to a light brown on the abdomen and back. The naevus occupied the lateral half of the right thigh, being defined by a line passing from the anterior superior iliac spine to the medial side of the right knee. Below the right knee the distribution was irregular. It gradually merged into normally coloured skin on the dorsum of the foot. The right buttock and posterior surface of the right thigh were wholly covered by the naevus, which in its upper part extended across the natal cleft to end in an irregular vertical line on the medial side of the left buttock. Compared with the right lower

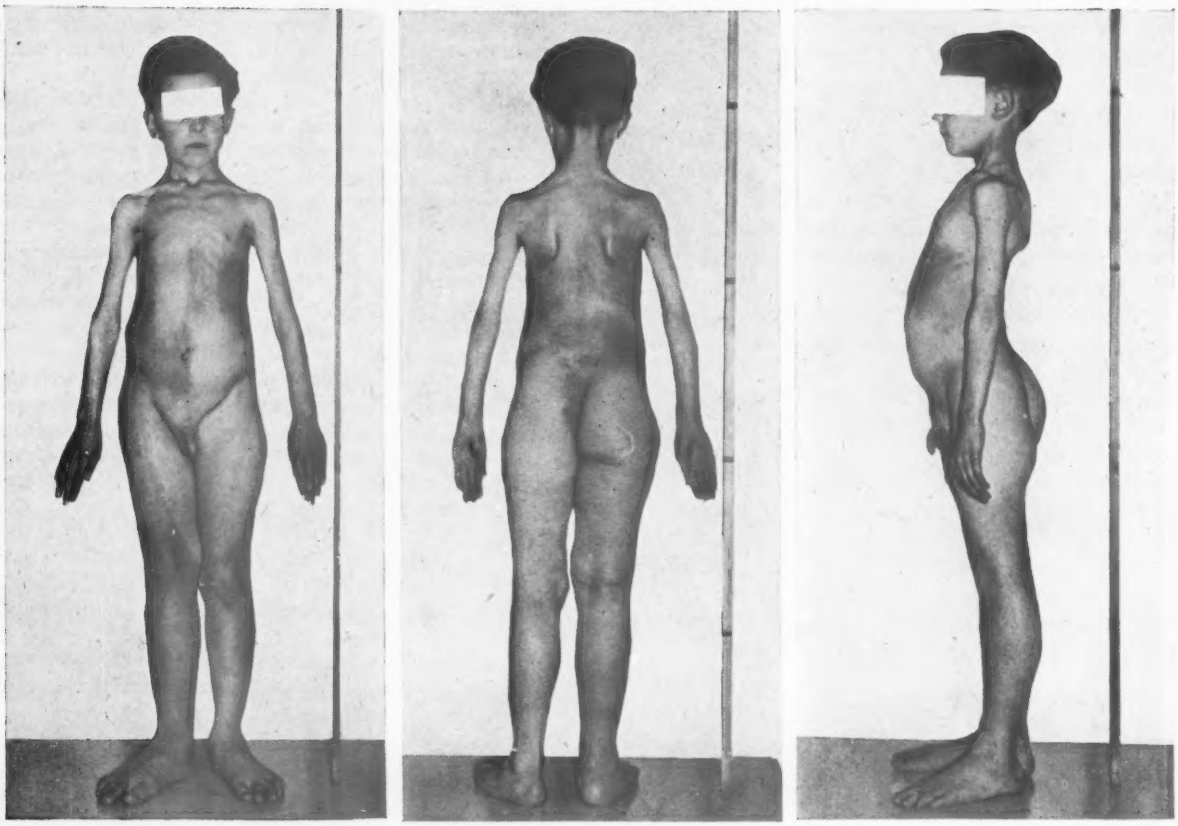

FIG. 1 FIG. 2 FIG. 3

FIGS. 1, 2, and 3.—Different postures showing asymmetry of lower limbs and extent of naevus.

FIG. 4.—Photograph showing difference in size of feet.

limb, the left was little affected. On the posterior surface of the left thigh there were several faint pink areas 1 to 2 in. in diameter. The naevus covered the whole lower right quadrant of the abdominal wall ending abruptly at the midline, and extending upwards on to the right side of the chest and right axilla. A large patch occupied the lower part of the left chest and loin. Anteriorly, a fainter area extended to the midline over the lower sternum and epigastrium. Irregular patches were present over most of the back from mid-scapula to the coccyx. A small deeper pigmented patch was situated over the sacrum. The skin of the upper limbs, scalp, face, neck, and scrotum was normal. When both lower limbs were cold the naevus on the right lower limb became deeper in colour and the whole limb appeared cyanotic. The colour became pinker when the limb was warmed (Figs. 1, 2, 3, 4).

Over the right lower costal cartilages there was a smooth subcutaneous mass 3 in. in diameter having the characteristics of a lipoma. A more diffuse mass of similar consistency covered most of the left side of the abdominal wall. A third lipoma was in the right spermatic cord. The skin overlying these three tumours was not involved by the naevus.

There were dilated superficial veins on the lateral side of the right thigh, below and lateral to the right knee, and on front of the ankle. Those below the knee were raised above the skin surface. There was no pulsation over the abnormal veins. After standing for several minutes the dilatation of the veins increased, but rapidly subsided when the limb was kept horizontal.

Pulsation of the femoral arteries was palpable on both sides. On the right side the popliteal and dorsalis pedis arteries could only be felt with difficulty. Those of the left limb were normal. The skin of the right lower limb was warmer to the touch than the left. Skin temperature readings revealed that the right leg was consistently 1 to 2° F. warmer than the left.

The musculature of the right buttock and right lower limb was well developed but softer than that of the left side. Muscle power was equal on both sides. There was no oedema of the lower limbs. No thrills were felt and no murmurs were heard on auscultation over the lower limbs. There was no abnormality of sensation or sweating in either limb.

The pulse was regular, 90 beats per minute. The apex beat was palpable 2 in. from the midline in the fourth left interspace. There was no cardiac enlargement and the heart sounds were normal.

Blood pressure:

Right arm 108/62; left arm 110/60.
Right leg 130/80; left leg 132/80.

No abnormal signs were found in the respiratory system. There was no enlargement of the abdominal viscera.

No abnormalities were detected in the cranial nerves. The tendon reflexes were normal in the upper and lower limbs. Abdominal reflexes were present. Plantar reflexes were flexor. The optic discs and vessels were normal.

Investigations. X-ray films of the lower limbs showed that there was elongation of all bones of the right limb compared with the left. There was thickening of the cortex of the right femur and tibia (Figs. 5, 6, and 7). Films of the skull, upper limbs, spine and pelvis were normal. A radiograph of the chest showed a normal cardiac outline, no cardiac enlargement, and normal lung fields.

Arteriograms were performed on both lower limbs, 20 ml. 50% diodone being introduced into each femoral artery. No evidence of an abnormal arteriovenous communication was obtained in either limb. It was, however, seen that the superficial veins of the right limb were more dilated than normal.

The oxygen content of blood withdrawn from the right femoral artery and vein, and the right basilic vein was determined. The results were as follows:

	Oxygen Content (vols. %)	Oxygen Saturation (%)
Saturated blood	20·73	100
Right femoral artery ..	17·8	86·4
Right femoral vein ..	13·4	64·5
Right basilic vein	15·3	73·9

An electrocardiogram showed no abnormality.

The effect of sudden occlusion of the right and left femoral arteries on the pulse rate was observed. A sphygmomanometer cuff was applied at a pressure of 160 mm. Hg to each thigh in turn, a continuous electrocardiographic record being taken before and during occlusion. There was no slowing of the heart after occlusion of each femoral artery.

The effect of occlusion of the femoral arteries on the blood pressure in the upper limbs was also observed. The upper limb pressures remained unaltered after a pressure of 160 mm. Hg had been applied to each thigh in turn.

The Wassermann and Kahn reactions were negative. A blood count and urine analysis were normal.

MEASUREMENTS OF THE LIMBS

	Right (in.)	Left (in.)
Anterior superior iliac spine to medial malleolus	27¼	26
Anterior superior iliac spine to medial epicondyle femur	15	14½
Medial epicondyle femur to medial malleolus	12¾	12¼
Knee (circumference)	12¼	11¼
Thigh (circumference 4 in. from medial epicondyle of femur) ..	14½	13
Calf (circumference 4 in. from tibial tubercle)	12¼	11
Foot (sole from os calcis to tip of second toe)	10	8¾
Foot (dorsum from medial malleolus to tip of second toe)	8¼	7

FIG. 5

FIG. 6

FIG. 7

FIGS. 5, 6, 7.—Radiographs of lower limbs, showing elongation of bones of right side.

Discussion

Clinical Features. The cardinal features of haemangiectatic hypertrophy are hypertrophy of a limb, the frequent occurrence of cutaneous naevi and abnormalities of the vessels in the affected limb.

Hypertrophy. Trélat and Monod (1869) observed that most often the enlargement of the limb is generalized, there being an increase in both length and in girth. The enlargement is seen at birth or in the first few months of life, but may escape notice until the child begins to walk. In spite of the enlargement the configuration of the limb remains more or less normal, gross deformity only being seen in the rarer types where hypertrophy is partial and limited to the hand or foot. Most commonly one leg is affected, an upper limb less often. Hemihypertrophic forms in which an arm and leg on one side are enlarged have been described by Parkes Weber (1907), Cagiati (1907), Gougerot and Filliol (1929), Downing (1933), Reichenheim (1943), Lian and Alhomme (1945). In these there may also be involvement of the skull and thorax on the affected side. Crossed forms in which an arm and a leg on opposite sides of the body are enlarged appear to be very rare, as do those in which both legs are affected. An example of the latter is described by Lian and Alhomme (1945). Eventually the bones of the limb show some lengthening. Radiologically there is little change in the bone structure except for the increase in length. The cortex of the long bones may be thickened. In the later stages generalized osteoporosis may occur. Occasionally phleboliths are seen as described by Freund (1936), Ward and Horton (1940). Depending on the extent to which a lower limb is lengthened, there is a compensatory scoliosis of the vertebral column with upward tilting of the pelvis on the affected side. Lian and Alhomme (1945) describe the rare complication of dislocation of the hip on the lengthened side.

Hypertrophy of the soft tissues usually involves muscles, connective tissue, and fat. The peripheral nerves are not affected but the occasional occurrence of neurofibromatous tumours akin to the plexiform tumour of von Recklinghausen's disease has been reported (Louis-Bar and Legros, 1946). Muscular power may be increased in the hypertrophic limb but this is inconstant. Visceral enlargement has been described in the hemihypertrophic type, as in the case of Cagiati (1907), in which enlargement of the viscera on the left side of the abdomen accompanied hypertrophy of the left upper and lower limbs. When the face is involved there may also be hemihypertrophy of the tongue (Gougerot and Filliol, 1929).

Cutaneous Manifestations. The cutaneous naevus is usually of the naevus flammeus or ' port-wine stain ' type, which is present at birth. Occasionally small, pigmented, nodular haemangiomata may be found on the naevus or the adjacent skin. The naevus varies in colour from deep red to a faint pink or brown which may be hardly distinguishable from the normal skin. Gray (1928) described an unusual form of naevus in which pigment was present in the basal cell layer of the epithelium.

There is great variation in the size and distribution of the naevus. Adams (1858) recorded that the naevus may end abruptly at the medial line of the body, an observation which has since been frequently made. Most often the enlarged limb is affected but its occurrence in other sites has been reported. Gougerot and Filliol (1929) maintain that there is no constant correlation between the site of the naevus and the limb involved. The naevus often roughly corresponds with the distribution of the sensory nerve roots, and Lian and Alhomme (1945) remark on its resemblance in shape to the eruption of herpes zoster. The edges are usually irregular but may fade imperceptibly into normal skin.

The skin of the affected limb is usually normal in texture but may be dry and scaly, becoming atrophic or indurated in the later stages. The skin temperature is often raised over the limb, and the sweat glands may be over-active (Klippel and Trenaunay, 1900; Gougerot and Filliol, 1929). Cutaneous sensation is usually normal. Subcutaneous lipomata are a somewhat rare finding and have been reported by Friedberg (1867) and Reichenheim (1943).

Blood Vessels. The vascular defects in haemangiectatic hypertrophy vary from simple dilatations of the veins to true arteriovenous communications.

Varicose veins are common in all varieties of haemangiectatic hypertrophy. They may be present at birth, but more often develop during childhood or early adult life. The onset of puberty may coincide with an increase in their number or sometimes with their first appearance. Their presence is, however, no indication of any underlying defect of the arterial system. Clinically the varicosities resemble those occurring in later life, but the local manifestations may be more severe. Ulceration of the overlying skin is common, often to be followed by severe haemorrhage. Treatment of the varicose veins is rarely successful. Extensive ligation or excision of veins is of little effect. Lian and Alhomme (1945) mention that sclerosing agents in higher concentrations than are usual may be tried. Their effect is only palliative.

The clinical features of arteriovenous communications are often inconspicuous. Thrills and bruits over the affected limb are uncommon, in contrast to their frequent occurrence in traumatic fistulae.

This is probable because the communication is so small. Rarely, the heart is enlarged. Ward and Horton (1940) found cardiac enlargement in only two of their 33 cases of congenital communications in children. There are some signs which may be helpful in the diagnosis of these communications. Nicoladoni (1875) and Branham (1890) observed that compression of the artery proximal to the communication may result in a decrease in pulse rate, the so-called ' bradycardiac reaction.' It is also known (McGuire, 1935) that both the systolic and diastolic blood pressures elsewhere in the body may be increased following closure of the arterial component of the fistula. Horton (1933) introduced the use of arteriography in the detection of these communications. In the same paper he drew attention to the value of estimating the oxygen saturation of the venous blood proximal to the communication. The venous blood will in such a case contain more oxygen than normal, and is evidence of the passage of arterial blood directly into the vein.

Aetiology. The presence of these various anomalies at birth is suggestive of some causative agent acting on the embryo in the early stages of its development. It is unusual for there to be evidence of any inherited factor in the production of the disease. Lian and Alhomme (1945), however, describe an example of the Klippel-Trenaunay syndrome in a young man whose father, uncle, and grandfather all had congenital varices affecting one limb. The uncle also had hypertrophy of one side of the thorax.

Louis-Bar and Legros (1946) suggest that haemangiectatic hypertrophy is an allied condition to the Sturge-Kalischer-Weber syndrome of cerebral angioma accompanied by a facial naevus. Parkes Weber (1947) considers that the latter condition and similar ' telangiectatic and angioma-like dysplasias ' are caused by some ' accidental ' local injury to the embryo during early intra-uterine life. Louis-Bar and Legros (1946) draw attention to other conditions in which hypertrophy of a limb may be an occasional occurrence, such as neurofibromatosis of von Recklinghausen and tuberose sclerosis. They consider that these conditions may be related to the haemangiectatic hypertrophies.

Congenital syphilis has been invoked as a cause, but the presence of positive serological reactions as in the cases of Beatty (1927) and Gougerot and Filliol (1929) appears to have been fortuitous. Increase in the local blood supply to the part has been held responsible for the hypertrophy. Klippel and Trenaunay (1900) thought that the cutaneous naevus may be responsible for this increased supply, but they recognized that the naevus was not invariably present on the enlarged limb. In the case of experimental arteriovenous communications there is some evidence that an increase in blood supply to the limb may lead to hypertrophy (Holman, 1937). Both Reid (1925) and Horton (1934) considered that the increase in bone length in the presence of a congenital arteriovenous communication is caused by an increase in blood flow to the growing end of the bone before closure of the epiphyses. Horton (1934) showed by arteriography that when the bone was lengthened an arteriovenous fistula may be in close apposition to the epiphyseal line.

Servelle (1945; 1947) has claimed that the overgrowth of bone in the Klippel-Trenaunay syndrome may be due to venous stasis. He has shown in many cases that the venous pressure is raised, and demonstrated by venography that the venous circulation may be obstructed by a congenital defect such as a fibrous band. He considers that symptomatic relief may follow removal of the obstruction.

Summary

A case is described of enlargement of both lower limbs associated with an extensive cutaneous naevus and varicose veins in a boy aged seven years.

This patient exhibited the three features of the Klippel-Trenaunay syndrome: hypertrophy, naevus, and varicose veins. His condition was unusual in that both lower limbs were affected. It is also of interest that his mother developed varicose veins at an early age, which have proved intractable to treatment.

There was little evidence in favour of there being a congenital arteriovenous communication in either lower limb. No thrills or bruits were detected. The blood pressure in both lower limbs was the same and not abnormally raised. There was no cardiac enlargement. There was no bradycardiac response on occlusion of each femoral artery. The oxygen content of the venous blood from the right lower limb was normal. An arteriogram showed no evidence of an abnormal arteriovenous communication in either limb.

I have to thank Dr. T. Colver and Mr. Wilfred Hynes for permission to publish this case and for their encouragement. I am indebted to Mr. Clifford Jones and Mr. D. H. Randall for performing the arteriograms, to Dr. A. G. Macgregor for the oxygen estimations, and to Dr. T. Lodge for permission to reproduce x-ray films.

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THE RELATIONSHIP OF IDIOPATHIC CARDIAC HYPERTROPHY TO FOETAL ENDOCARDITIS

BY

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(RECEIVED FOR PUBLICATION, AUGUST 11, 1949)

Idiopathic cardiac hypertrophy in children may be divided into those cases associated with glycogen infiltration, and those without. A characteristic feature of the latter is the presence of gross fibro-elastic thickening of the endocardium (Kugel and Stoloff, 1933; Mahon, 1936). This thickened endocardium, frequently associated with myocardial scarring, has suggested that an inflammatory basis underlies the condition. Gross (1941), however, in a review of so-called foetal endocarditis, has brought convincing evidence against this concept, and attributes the myocardial changes to impaired nutrition secondary to the endocardial thickening.

The case presented here suggests that endocardial fibro-elastosis, which is found in 70% of cases of so-called foetal endocarditis (Gross, 1941) may, in cases surviving the neonatal period, lead to the condition of idiopathic cardiac hypertrophy in children, the myocardial hyperplasia being secondary to the endocardial thickening.

Case Report

P.D., a boy aged 21 months, was admitted to the Canadian Red Cross Memorial Hospital on Jan. 31, 1949, under the care of Dr. Reginald Lightwood. He died suddenly at the end of March, 1949, presumably from cardiac failure. He was an illegitimate child whose father was not known; the mother was healthy and there were no siblings. At birth, he was a normal baby weighing 7 lb.; he was breast fed for eight months and weaning was carried out normally. His early development was normal and he was walking at 15 months of age.

He had bronchitis and mild jaundice immediately after birth, and four attacks of bronchitis in the last year of his life. Fifteen months before he died he was in hospital with bronchopneumonia, and then was considered to be mentally backward. He had had no other illnesses.

One month before admission he started to cough, became fretful, and lost his appetite. Three days later he had a slight rise of temperature. This was unaffected by sulphonamides, but subsided while he was given oral penicillin. Two weeks later his face became puffy, and shortly afterwards his legs and hands also became swollen. On Jan. 28, three days before admission, his abdomen was enlarged and he was rather breathless. At this time he vomited occasionally after food.

On admission the baby was pale, apyrexial, orthopnoeic, and slightly cyanosed. There was considerable oedema of the face, hands, forearms, abdominal wall, legs, and sacral region, and ascites. Slightly enlarged glands were palpable in both axillae and in both posterior triangles of the neck. The throat was not inflamed. The apex beat was not palpable, and the area of cardiac dullness was increased both to the left and to the right. The heart sounds were muffled and there was a soft systolic murmur at the apex. There was no pericardial friction. The pulse was of low tension (125 per minute). The jugular venous pressure was raised 7 cm. above the sternal angle at

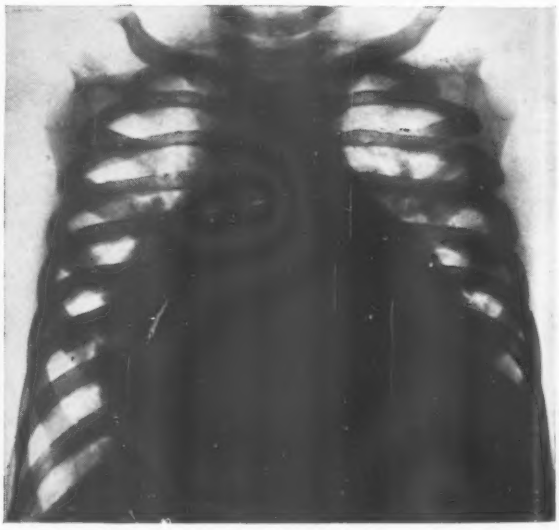

FIG. 1.—Radiograph of chest showing gross enlargement of the cardiac shadow.

45°, but no jugular pulsation was visible. The blood pressure was 90/65. There were diffuse rhonchi in all areas over both lungs, and the respiration rate was 40 per minute; there was diminished air entry at the left base. The liver was enlarged 6 cm. below the costal margin in the mid-clavicular line. The fundi were normal. A radiograph of the chest showed generalized enlargement of the cardiac shadow suggestive of pericardial effusion (Fig. 1); screening of the heart showed no evidence of cardiac pulsation except for a small area at the upper left border. The electrocardiogram showed normal standard leads and upright T waves in leads V1 and V2, and the corrected Q-T interval was 0·410 sec. (Fig. 2). The urine showed 45 mg.% albumin and a few epithelial cells; subsequently there was no other abnormality and usually no albuminuria. The red blood count was 3·9 million with 11·7 g. haemoglobin. The white blood count was 13,800 with 26% polymorphs, 68% lymphocytes, 5% monocytes, and 1% eosinophils. The serum protein level was 4 g. %, and the albumin-globulin ratio 1 : 1. The serum urea level was 57 mg. % and the serum cholesterol level 500 mg. %. The antistreptolysin titre was less than 50 units per ml. A tuberculin jelly and Mantoux test (1 : 1,000) were both negative.

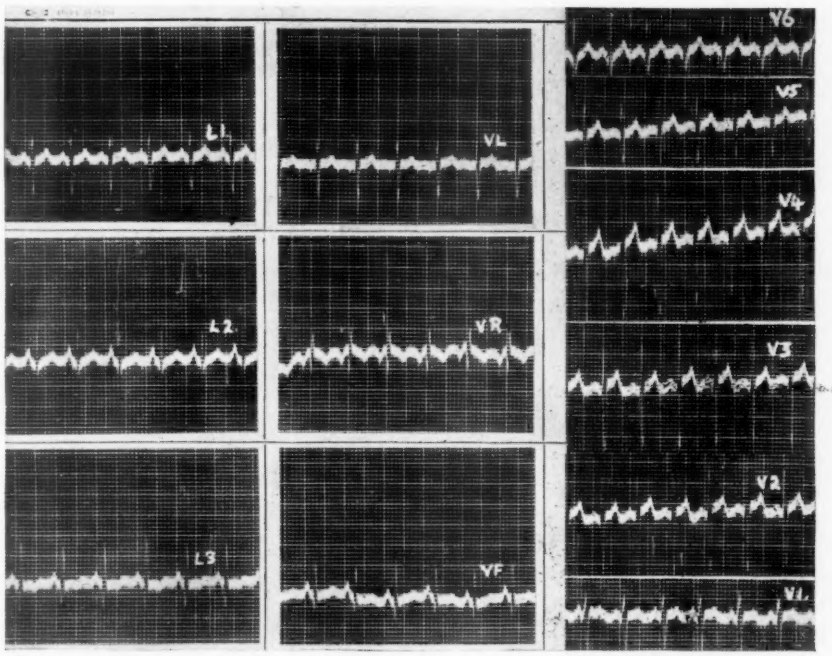

FIG. 2.—E.C.G. taken on admission showing normal standard leads and upright T waves in leads V1 and V2.

Progress. A week after admission oedema was less, but the jugular venous pressure was still raised, and the liver was enlarged 6 cm. Tachycardia of 100-130 persisted throughout the illness. During the first fortnight in hospital the baby lost 6 lb. in weight and the oedema almost completely disappeared, after which it became evident that there was generalized muscular wasting. The heart and liver did not alter materially in size. One month after admission he developed a respiratory infection which was treated with penicillin, and a week later generalized oedema recurred. An attempted aspiration of the pericardium was unsuccessful on three occasions, and the impression was gained that the pericardial sac was not thickened. Two months after admission fluoroscopy showed the heart shadow unaltered in size and without any obvious pulsation, but the appearances were believed to be compatible with gross cardiac dilatation. A tentative diagnosis of glycogenic cardiomegaly was made, and investigations for glycogen storage disease performed. The fasting blood sugar was 84 mg. %, and 15 minutes after the injection of adrenaline the blood sugar was 78 mg. %. The urine had a trace of acetone in it, but no sugar. The colloidal gold and thymol turbidity tests were both slightly positive. There was an improvement in the anaemia after the first two months of the illness, but leucocytosis persisted throughout. His appetite was good throughout the illness. The patient died suddenly, exactly three months after admission, while being washed in bed.

Post-mortem Report

The subject was a male infant of average build and a fair state of nutrition, with no external evidence of developmental abnormality.

Heart. (Weight, 140 g.) The heart was considerably enlarged owing to hypertrophy of both ventricles, especially the left. The parietal pericardium was firmly adherent to the anterior surface of the right ventricle and to the right auricular appendage. There was no evidence of recent pericarditis. The pericardial fluid was clear and of normal volume. The endocardium of both ventricles was strikingly thickened and opaque and very conspicuous around the hypertrophied muscle trabeculae. The mitral and tricuspid valves showed unusual translucence, with possibly myxomatous nodules 1-3 mm. in diameter projecting from the free edge of the cusps (Fig. 3). No rheumatic vegetations were seen. The aortic and pulmonary valves were normal. The right auricle was considerably dilated and the appendage filled with

FIG. 3.—The heart opened to expose the right side of the interventricular septum and the tricuspid valve. Note the nodular thickening towards the free margin of the septal cusp, and the endocardial thickening, especially on the septum.

ante-mortem thrombus. The foramen ovale and the ductus arteriosus were both closed. The coronary vessels and the aorta were healthy.

Valve measurements:
Aortic, 40 mm. Mitral, 58 mm. Tricuspid, 72 mm. Pulmonary, 54 mm.
Thickness of ventricles:
Left ventricle, anterior, 9 mm.; posterior, 10 mm.; Right ventricle, anterior, 3·5 mm.; posterior, 4·5 mm.

Lungs. (Weight: right, 135 g.; left, 110 g.) There was about 50 ml. of slightly cloudy, yellow fluid in the left pleural cavity. Some old fibrous adhesions were found between the right lower lobe and the diaphragm. Both lungs were well expanded, but firmer than normal in consistency and slightly rusty brown in colour. There was moderate oedema in the right upper lobe but not elsewhere. Frothy fluid was found in small quantities in the trachea and bronchi. The hilar glands were not enlarged.

Liver. (Weight, 345 g.) This organ was a little above average size, pale yellowish brown, with the lobular markings accentuated. The sectioned surface showed the bright orange yellow colour of the periportal zones, contrasting with the greyish brown, slightly depressed centrilobular zones. The consistency was firmer than normal, and the organ cut with a distinctly fibrotic resistance. The gall bladder, bile ducts, and pancreas were normal.

The spleen (weight, 32 g.) was normal.

The kidneys, a little above average size, were pale but otherwise normal, as also were the pelves, ureters, bladder, and genitalia.

The thyroid, thymus, and adrenals were normal.

The alimentary canal was normal. A very considerable quantity of clear yellow fluid was found in the general peritoneal cavity.

The brain (weight, 960 g.) was normal.

Histological Examination. The following findings are recorded:

MITRAL VALVE AND LEFT VENTRICLE. There was marked hypertrophy of the subendothelial trabeculae and considerable thickening and elastosis of the endocardium (Fig. 4), with no evidence of inflammation except in the pericardium. In some places encroachment into the myocardium had occurred with atrophy of the muscle fibres. There was no inflammation in the valve.

TRICUSPID VALVE AND RIGHT VENTRICLE. There was no evidence of valvulitis, but considerable hypertrophy of the muscle trabeculae and thickening of their endocardium. The pericardium was chronically inflamed with moderate hyperaemia, lymphocyte and plasma cell infiltration. There was endocardial thickening, very rich in elastic fibres. Moderate sized branches of the coronary arteries showed intimal thickening with elastic reduplication.

TRICUSPID CUSP. There was myxomatous swelling

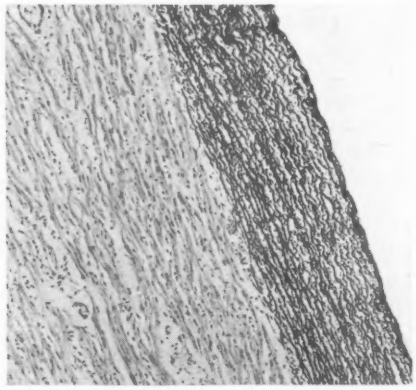

FIG. 4.—Section of left ventricle showing fibro-elastosis of the endocardium. (Weigert's elastic stain and neutral red. × 65.)

at free margin, but no evidence of inflammation (Fig. 5).

LEFT AURICLE. The endocardium was much thickened with striking elastosis, and there was chronic inflammatory thickening of the pericardium. The visceral pericardium showed striking papillary proliferation near the attachment of the parietal pericardium.

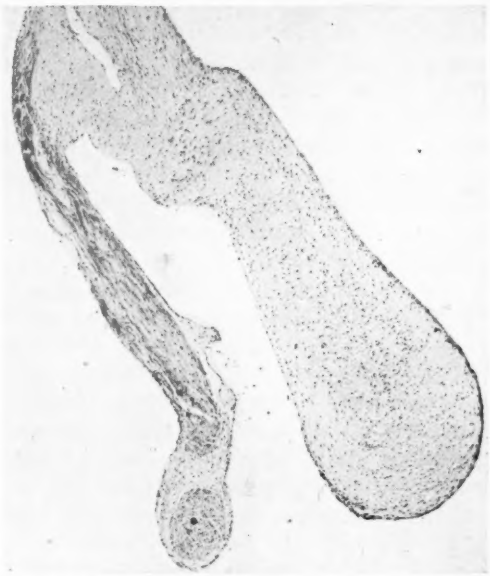

FIG. 5.—Section through a cusp of the tricuspid valve showing the myxomatous nodular thickening of the free margin. Note the absence of any inflammatory infiltration. (Haematoxylin and eosin. ×25.)

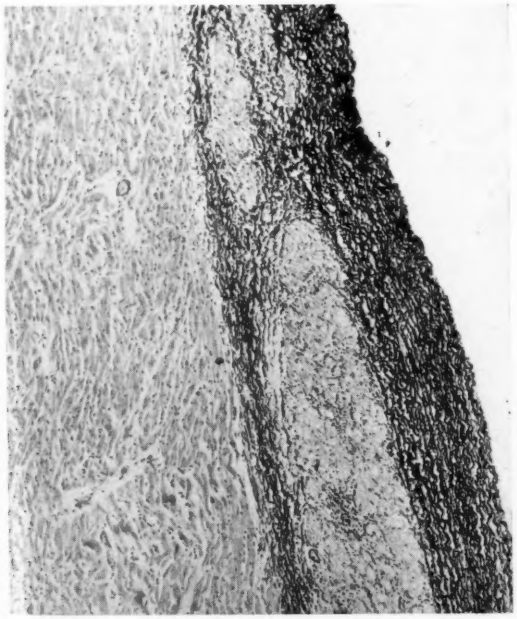

FIG. 6.—Section of the interventricular septum showing the great thickening of the endocardium, and the striking elastic hyperplasia. Embedded in this thickened endocardium are bundles of Purkinje-like fibres. (Weigert's elastic stain and neutral red. ×55.)

RIGHT AURICLE. The endocardium was not thickened. The serous pericardium was thrown into papillary folds in the angle of reflexion onto the parietal layer.

RIGHT AURICULAR APPENDAGE. Extensive, adherent ante-mortem thrombus showing early organization was shown.

INTERVENTRICULAR SEPTUM. The endocardium on the right surface was much thickened, and contained bundles of vacuolated swollen cardiac muscle fibres in its middle layer (Fig. 6). A striking elastic hyperplasia in the superficial and to a less extent in the deep layer of the endocardium was seen. Coarse granules of polysaccharide, presumably glycogen, were conspicuous in the endocardial muscle fibres, but not elsewhere in the myocardium (Fig. 7).

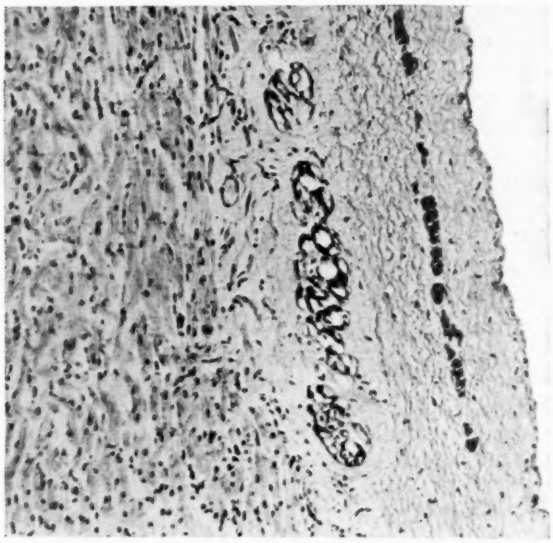

FIG. 7.—Thickened endocardium on the right surface of the interventricular septum. Bundles of fibres with central vacuole and ring of glycogen are seen in cross section in the deeper part of the endocardium. The ordinary myocardial fibres are not vacuolated. (Glycogen stain. ×90.)

AORTIC VALVE. The ground substance was myxomatous. There was no valvulitis.

PAPILLARY MUSCLE. The endocardium was thickened with severe elastosis, especially towards the apex.

LIVER. The centrilobular zones showed passive congestion, hydropic and fatty degeneration and necrosis. The periportal zone cells were infiltrated with glycogen. The portal tracts were unusually conspicuous because of lymphocytic infiltration,

bile duct proliferation, and fibrosis, especially in the left lobe. The capsular lymphatics were distended.

SPLEEN. Lymphoid hyperplasia and passive congestion were seen.

KIDNEY. Eosinophil reticular material was found in the capsular spaces, and several foetal type glomeruli.

Discussion

It is apparent that the hypertrophy in the heart in this case is not due to glycogen infiltration, as the muscle fibres lack the vacuolated appearance characteristic of that condition (Pompe, 1933; Finkelstein, 1936; Carrington and Korumbhaar 1924). Moreover, the staining for polysaccharide substances showed negligible amounts of glycogen in the myocardial fibres. This was not due to faulty technique, as the persisting Purkinje fibres gave a characteristic and quite heavy reaction for glycogen (Fig. 7). The positive adrenaline test was probably due to the fact that the adrenaline was not properly absorbed owing to the gross oedema; and the liver glycogen was consistent with the appearances usually seen in children in cases of sudden death (Bodian, personal communication).

A survey of the literature reveals quite clearly that endocardial elastosis is not a feature of glycogenic cardiomegaly (Finkelstein, 1936; van Creveld and van der Linde, 1939; Pompe, 1932; Antopol and others, 1934; Humphreys and Kato, 1934). In marked contrast are the findings in the non-glycogen group of cases of idiopathic cardiac hypertrophy, in which almost all those published have shown gross endocardial thickening (Kugel and Stoloff, 1933; Levine, 1934; Mahon, 1936; Weinberg and Himelfarb, 1943; Vulliamy, 1947).

In Gross's review of the literature on so-called foetal endocarditis, he mentions that 70% of cases show fibro-elastic thickening of the endocardium. As endocardial elastosis is rare, it is all the more noteworthy that it should occur in both these conditions, hitherto considered to be separate entities. This strongly suggests that idiopathic hypertrophy of the heart is a late result of so-called foetal endocarditis in cases surviving the neonatal period. On this hypothesis, idiopathic hypertrophy of the myocardium is probably a work hypertrophy resulting from interference with normal heart action. The precise mechanism is not clear, but the presence of a thick fibro-elastic endocardium must impede diastole and systole. In diastole, the elasticity of the thickened endocardium will impose a resistance to cardiac filling. In systole, it might appear at first sight that the elastic recoil would assist emptying of the heart; however, the systolic wave occurs from apex to base, and any superadded contraction out of step with the normal sequence must cause a resistance to cardiac outflow.

Despite the macroscopic finding of nodular thickening of the valves, no evidence of inflammation was found in our case, the thickening consisting merely of myxomatous tissue of embryonic appearance (Fig. 5). This, together with the absence of cellular infiltration in the endocardium, strongly supports Gross's contention that so-called foetal endocarditis is not of inflammatory origin. It also serves to differentiate the condition from Fiedler's myocarditis, in which there are acute inflammatory changes in the interstitial tissue of the heart. The occasional finding by other observers of lymphocytic infiltration in the myocardium (Kugel and Stoloff, 1933) can be explained by Gross's theory to be a result of myocardial damage due to nutritional interference by a thickened endocardium. Dissmann (1932) has suggested that the endocardial changes represent a primary developmental defect; the persistence in our case of Purkinje fibres within the thickened endocardium, indicative of the early stage at which the change takes place (Robb, Kaylor, and Truman, 1948), lends further support to this view.

Summary

The phenomenon of fibro-elastic hyperplasia of the endocardium in idiopathic cardiac hypertrophy and in so-called foetal endocarditis is discussed. A relationship between these two conditions is suggested largely on the basis of this common finding, and it is illustrated by a fatal case of endocardial fibro-elastosis with myocardial hypertrophy in a boy aged 21 months.

We are indebted to Dr. Paul Wood and Dr. Martin Bodian for their advice, and to Dr. Reginald Lightwood for permission to publish this case and for his helpful criticism.

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COARCTATION OF THE AORTA (ADULT TYPE) WITH RUPTURE DISTAL TO THE COARCTATION

BY

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(Received for Publication, August 9, 1949)

Coarctation of the aorta is by no means an uncommon lesion. Two types are generally recognized (1) the infantile, in which there is a diffuse narrowing of the aorta between the origin of the left subclavian artery and the insertion of the ductus arteriosus, and (2) the adult type, in which the area of constriction is very narrow, and is situated at or close to the site of insertion of the ductus.

One of the most frequent causes of death is rupture of the aorta. As this is usually proximal to the coarctation it seemed of interest to report the following case of rupture distal to the coarctation, and to review similar cases previously reported.

Case Report

The patient, a boy aged 4 years, the third of three children, was born of healthy parents. There was no history of rubella during the pregnancy and birth was normal and at term, the weight being 7 lb. 3 oz. Development was normal. The only previous illness was measles at 1 year and the child also had occasional ' blue turns ' associated with displays of temper. One month before admission to hospital the child had a mild attack of bilateral otitis media, and eight days before admission the present illness began with a gradual onset of lassitude and anorexia which persisted. On the third day a moderate degree of tonsillitis was found. Attacks of fever accompanied by profuse sweating and preceded by shivering, pallor, and increased lethargy then began. The attacks lasted about two hours and recurred several times a day until admission. The child was sometimes delirious in these attacks. The temperature fluctuated between normal and 102° F. An unrecorded amount of sulphathiazole was given on the sixth, seventh, and eighth days. During this period there was no coryza or cough and no evidence that the child had been in pain.

On admission on the eighth day of his illness the child was pale and listless (temperature, 100° F.). His weight was 42 lb. 6 oz. and development and nutrition were normal for his age. The tongue was coated but moist and mild tonsillitis without exudate was present. There were no petechiae and the spleen was not palpable. No abnormality was found in the abdomen, the respiratory, or central nervous systems. There was marked arterial pulsation in the suprasternal region and capillary pulsation was seen in the nail beds. The radial pulses were equal and of high tension. No pulsation could be elicited in the femoral, dorsalis pedis, or posterior tibial arteries. The blood pressure in both arms was 150/100 mm. Hg. The pressure in the lower limbs was not recorded. Vigorously pulsating vessels were easily palpable in the supra- and infrascapular regions, along the vertebral border of the scapula, and running along the lateral thoracic walls; systolic bruits were audible over the courses of these arteries. The deep epigastric arteries were not palpable.

The apex beat was maximal in the fourth intercostal space in the nipple line and was not markedly forcible; no thrills were palpable and percussion did not suggest any enlargement of the base of the heart. Well-marked, rough systolic murmurs of approximately equal intensity were heard at the apex and in the second and third spaces to the left of the sternum, the former being conducted slightly to the axilla; a short diastolic murmur was audible at the apex. The rhythm was normal.

Investigations. The urine was normal.

A throat swab on culture yielded only a scanty growth of *Strep. viridans*, diphtheroids, and *N. catarrhalis*.

Blood tests gave the following results:

E.S.R. 36 mm. in one hour.

Haemoglobin 82% (Haldane).

Red blood count, 3,900,000 per c.mm. C.I. 1·05.

White blood count, 14,000 per c.mm.; stab forms 14% (1,960 per c.mm.); polymorphonuclear leucocytes 53% (7,420 per c.mm.); eosinophils 4% (560 per c.mm.); lymphocytes 26% (3,640 per c.mm.); monocytes 3% (420 per c.mm.).

Blood urea, 22 mg. per 100 ml.

Blood cultures on the twelfth and thirteenth days were negative.

Dr. C. J. C. Hodson reported on a radiograph of the chest (Fig. 1) as follows:

' There is a moderate degree of cardiac enlargement affecting mainly the left ventricle. The aorta is left-sided.

There is a vague blurring in the region of the arch which makes it impossible to assess its true size, but it would appear to be enlarged. The pulmonary

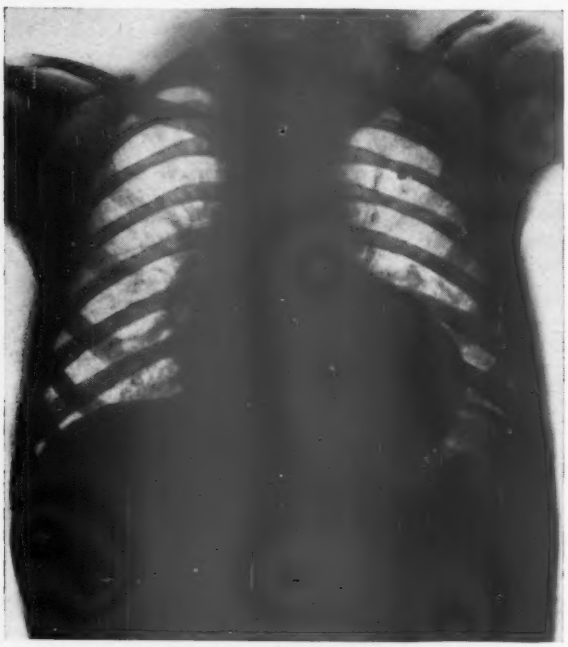

FIG. 1.—Postero-anterior view of chest showing blurred shadow in the aortic region.

vessels on the whole are less well developed than usual. No rib notching is seen. The left ventricular enlargement suggests an aortic or hypertensive lesion. But there is no definite sign, radiologically speaking, which gives the cause of this.'

Course of Illness. The temperature became normal for 12 hours following admission but rose again and continued to fluctuate between 98·4° F. and 102° F. during the next four days, the pulse and respiratory rates averaging 105 and 28 per minute respectively. On the thirteenth day slight clinical deterioration was accompanied by increased tachycardia. Intramuscular penicillin, 80,000 units four-hourly, was given after the second blood culture. Pyrexia continued next day and profuse sweating became frequent. There was some frequency of micturition but the urine showed only an occasional red or pus cell.

On the sixteenth day at 1 p.m. the child had a sudden paroxysm of coughing, became dyspnoeic, and sat up complaining of a pain referred to the right side; he cried and seemed distressed. He had a hoarse, croupy cough with some dyspnoea, and a moderate degree of inspiratory stridor which could not be definitely localized to the trachea or bronchus. There was moderate intercostal and subcostal recession with evidence of slight mediastinal displacement to the left. There was impairment of the percussion note and diminished air entry in the region of the left lower lobe and coarse rhonchi, mainly expiratory in nature, were heard over all areas of the chest. The child was not cyanosed or greatly distressed and slept at intervals. At 2 a.m. on the seventeenth day, another bout of coughing occurred during which about 12 oz. of fresh blood came from the mouth; moderate peripheral circulatory collapse followed. A slow transfusion of blood and morphine gr. 1/12 were given. During the succeeding hours the condition improved slightly though the stridor increased and the rib recession became more marked, particularly in the left basal region where it was associated with absent breath sounds. At 12.30 p.m. the child vomited another 10 oz. of fresh blood; peripheral circulatory failure and death followed shortly afterwards.

Post-mortem Examination

The post-mortem examination revealed only coarctation of the aorta just distal to an obliterated ductus

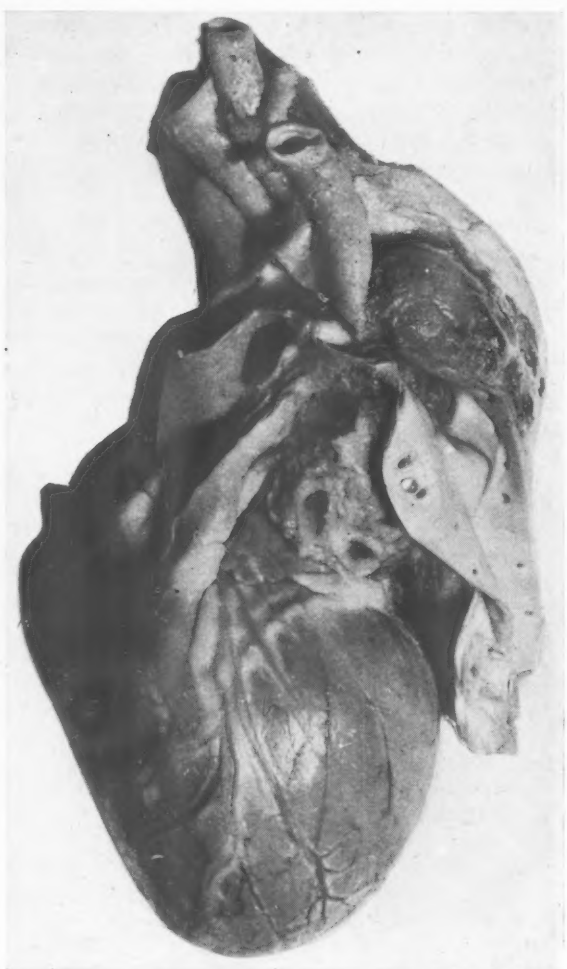

FIG. 2.—Heart and great vessels showing coarctation, tear of aorta, and false aneurysm.

arteriosus (Fig. 2), with infective endarteritis just beyond the coarctation and rupture forming a false aneurysm which had secondarily opened into the oesophagus.

The aneurysm was filled with infected thrombus, the infective process extending into the wall of the oesophagus. Recent blood clot was seen in both main bronchi and in the stomach, and the small intestine contained a little altered blood.

Aorta. The ascending aorta was moderately dilated, gradually narrowing from a diameter of 1·5 cm. at the aortic valve to 0·6 cm. at the origin of the left subclavian artery. Near the orifice of the left coronary artery was a small patch of atheroma extending upwards for 1·5 cm. as a narrow yellow streak. Immediately distal to the left subclavian artery the aorta was constricted by a circular shelf of tissue which projected into the lumen and reduced it to a tiny hole 2 mm. in diameter.

The obliterated ductus arteriosus was represented by a band of dense fibrous tissue, 1.3 cm. in length and 0·8 cm. thick, which was attached to the lower border of the arch of the aorta almost opposite the origin of the left subclavian artery 2 mm. on the proximal side of the constriction, and had produced a depression of the aortic wall 4 mm. in diameter.

Immediately beyond the coarctation, the aorta widened abruptly to a diameter of 0·9 cm. and remained approximately the same size throughout the remainder of its course. The descending aorta showed no evidence of atheromatous change. There was a transverse tear of the anterior wall of the descending aorta, 1·0 cm. in length and situated 1·3 cm. beyond the constriction, from which a longitudinal prolongation extended upwards to within 2 mm. of the stenosis. This tear produced an opening measuring 1·6 × 1·0 cm. Immediately beyond the coarctation the intimal surface of the aorta was roughened by a number of tiny vegetations extending to the upper edge of the tear. While this upper edge was jagged with adherent blood clot, the lower edge was smooth and merged imperceptibly into the wall of the aorta. The lumen communicated through the torn wall with a false aneurysm measuring 3·4 × 2·4 cm. and filled with both old and recent blood clot. It lay in the mediastinum between the aorta and the oesophagus, displacing the latter to the right, and extended posteriorly to the right of the aorta. Inferiorly, it reached almost to the level of the second posterior intercostal arteries, and superiorly to the origin of the left subclavian artery. The wall of the oesophagus was ruptured by a longitudinal tear 3·5 cm. in length, projecting from which was a haematoma measuring 4·2 × 2·4 cm. (Fig. 3).

Heart. The heart weighed 109 g., and the left ventricle showed well-marked, concentric hypertrophy, its wall having an average thickness of 1·5 cm. The left auricle was 3-5 mm. thick and its mural endocardium was thickened. The aortic valve was bicuspid, both coronary arteries arising behind the left anterior cusp. The anterior cusp of the mitral valve was generally thickened and there were two small patches of atheromatous thickening near its attachment to the mitral ring. The chambers on the right side of the heart, the pulmonary artery, and the pulmonary and tricuspid valves were normal. There was no evidence of infective endocarditis.

The left coronary artery was 0·6 cm. in diameter at its origin whilst the right coronary artery was 0·1 cm. in diameter. The innominate artery, 1·0 cm. in diameter, was of almost the same size as the arch of the aorta, and both the left common carotid and the left subclavian arteries measured 0·7 cm. in diameter. The first right posterior intercostal artery was dilated to 3 mm. at its origin and was then lost in the mediastinal blood clot. The other branches of the aorta were normal in size. No anomalous arteries were discovered.

Histology. The only abnormal findings in the structure of the aorta were in the regions of the coarctation and the tear, with the exception of slight intimal thickening and subintimal fatty change in those areas of the ascending aorta which macroscopically resembled atheroma.

FIG. 3.—Torn oesophagus with haematoma projecting into its lumen.

At the coarctation itself the projection into the lumen of the aorta showed normal media without any evidence of fibrosis or inflammatory exudation. The overlying subintimal connective tissue was thickened, especially on the distal side of the constriction where it extended over 3-4 mm. of the adjacent aorta. Near the upper limit of the tear in the aorta and about 3 mm. beyond

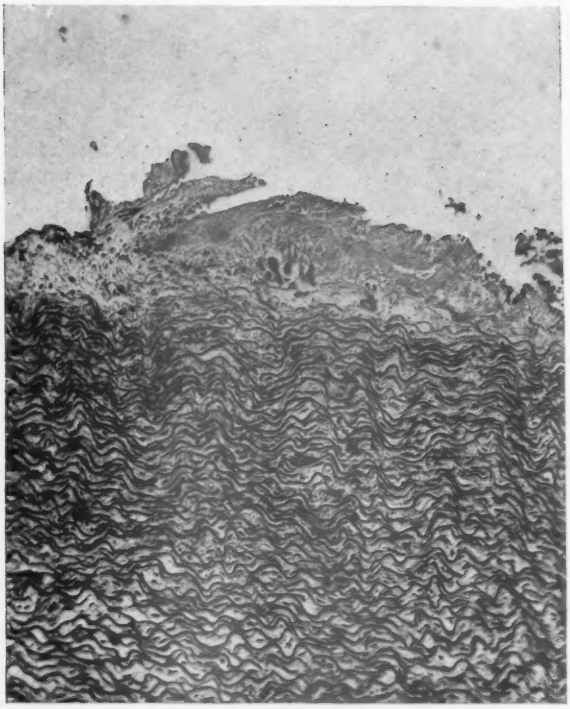

FIG. 4.—Section of aorta at the upper edge of the tear showing infective vegetation. × 80.

the coarctation the intima disappeared and was replaced by a small, raised, granular mural thrombus in which fragments of elastic tissue and collagen could be distinguished (Fig. 4). The thrombus contained numerous Gram-positive cocci and showed a slight polymorphonuclear infiltration at its edge, whilst in its deeper regions were collections of large, elongated necrotic cells mainly arranged at right angles to the surface.

In the vicinity of the tear and lying between normal medial tissue, there were definite zones where the elastic fibres were separated and the intervening muscle fibres and connective tissue cells showed fatty change and necrosis. Two such layers could be distinguished near the upper edge of the tear and one broad band lay centrally in the media at the lower edge. The bands began at the tear itself and extended for 2-6 mm. into the surrounding media. The areas were infiltrated by acute inflammatory cells, mainly neutrophil polymorphs with some eosinophils, which were most prominent in the zones adjoining the adventitia (Fig. 5). Here and there in the otherwise normal media were a few small nodules, superficially resembling Aschoff nodes, consisting of cells with round nuclei and indistinct cytoplasm. Wherever the aorta was in close contact with the mediastinal blood clot, the adventitia was disintegrated and infiltrated by an acute inflammatory exudate. The whole of the blood clot was heavily infiltrated with pus cells. Scattered throughout were fragments of elastic tissue and collagen with many small groups of Gram-positive cocci morphologically resembling staphylococci. These organisms were most noticeable in the superficial areas of the clot.

The ductus arteriosus showed normal obliteration of its lumen, but the surrounding connective tissue contained a moderate number of fibroblasts together with many small blood vessels and a light infiltration mainly of lymphocytes with some plasma cells. This process appeared to stop short at the aorta. There was no infiltration with similar cells or any inflammation in the aorta at the point of insertion and there was no evidence of spread of the fibrotic process to its wall.

The oesophagus was infiltrated with neutrophil polymorphs and a small number of eosinophils which were mainly found in the submucosa but in places they

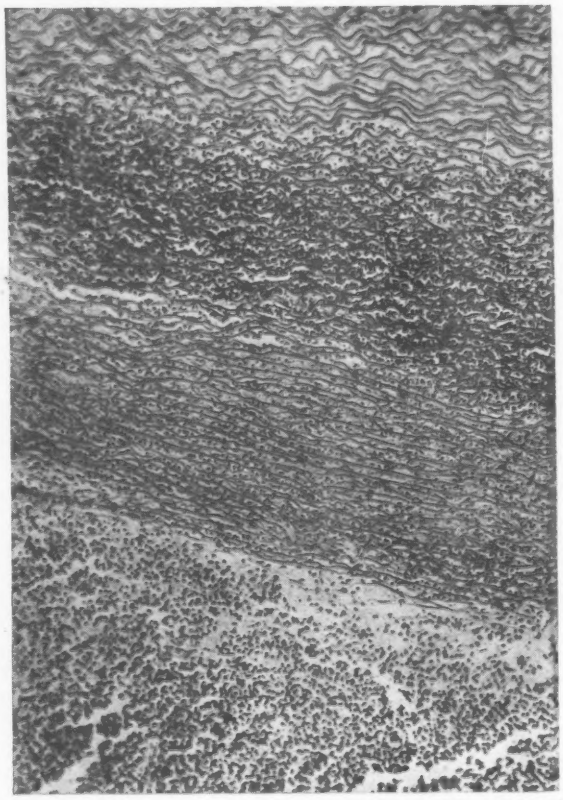

FIG. 5.—Section of aorta showing infected blood clot in the adventitia and inflammatory infiltration of the media. × 80.

extended into both muscle coats and the squamous epithelium.

Apart from slight general thickening, the aortic cusps appeared normal. The subendocardial tissue of the left auricle was greatly thickened and the myocardium of both the left auricle and ventricle was obviously hypertrophied.

The right auricle and ventricle, the mitral valve, the pulmonary, coronary, innominate, left common carotid and left subclavian arteries were all histologically normal.

Discussion

Clinical Findings in 13 Cases.—Clinical reports were available in 13 cases of rupture of the aorta distal to a coarctation. In seven the duration of symptoms was three months or less, while the remainder had had symptoms of cardiovascular disease for periods of four months to five years. In all but one of the latter cases, however, symptoms which could be attributed to serious aortic complications had been present for less than three months. The comparatively short history of a severe illness in these cases is in contrast to that found in uncomplicated cases of coarctation which generally present with fairly long and mild symptoms of hypertension or are discovered on routine examination. Periodic pain, often severe and apparently unrelated to effort, was a frequent complaint, occurring in eight cases; it was predominantly precordial in all of these but was sometimes referred to the left chest, shoulder, arm, or loin. Dyspnoea was reported to have been present for the duration of the illness in the same proportion of cases and to have occurred terminally in most. Cough, whether associated with respiratory infection or pressure upon the air passage, was a common finding. Haematemesis occurred terminally in seven cases, and in our patient was mistaken for a haemoptysis. Haemoptysis and painful dysphagia were also recorded, each in two instances. One patient presented with the clinical picture of dissecting aneurysm. The signs of coarctation in those cases in which it was diagnosed ante-mortem, did not differ from those found in uncomplicated cases. Aneurysms were apparent clinically in two cases on first examination, though one of these was possibly syphilitic in origin. Signs of poor aeration of the left lower lobe, presumably due to pressure on its bronchus, were mentioned in several cases, and haemothorax was present in three cases terminally.

When aortic endarteritis was present, the symptomatology was similar to that of bacterial endocarditis, but tended in some cases to be less well marked. In no case where rupture occurred were embolic lesions in the skin recorded, although they were frequently found in the spleen and kidney. On the other hand, in cases of endarteritis without rupture, petechiae and nodes were not uncommon and the signs of infection more definite. Endarteritis was possibly secondary to otitis media in one case, to dental extraction in another, and to tonsillectomy in a third; upper respiratory infection was present in several cases though it was not clear what relationship it bore to the onset of the endarteritis. Adequate chemotherapeutic or antibiotic prophylaxis is necessary before operations on these patients. Any unexplained pyrexia or illness must be regarded as possibly due to endarteritis.

It would appear that the symptoms of endarteritis in the presence of coarctation of the aorta are little different from those in bacterial endocarditis. Aneurysmal dilatation or impending rupture should be suspected when pains similar to those described above are a prominent feature.

The coarctation was diagnosed during life in six of the thirteen cases of rupture distal to the stenosis, while in seven cases of endarteritis without rupture a definite diagnosis of coarctation was made in only one case, though endocarditis had been suspected in all. Of the ten cases with radiological reports, the diagnosis was made in five.

Radiological Findings. Radiological findings were reported in 10 of the 13 cases. In four cases aortic aneurysms were visualized, one being situated 'at the left hilum,' one occupying most of the left upper zone and one 'at the right hilum'; the fourth, at the left hilum, was associated with a 'large aortic knob.' Two cases showed opacities in the left hilar region, one being associated with an absent aortic knob and the other with an opacity involving most of the left upper zone which at necropsy proved to be a large haematoma in the upper lobe. A widened ascending aorta was mentioned in two further cases and a 'large aortic knob' in another. In view of the necropsy findings in our patient, the unusual appearance in the aortic arch region probably represented the para-aortic haematoma. Since absence of the aortic knuckle is the usual finding in uncomplicated cases of coarctation, although it may be simulated by an enlarged left subclavian artery (Crafoord, 1945), these reports would suggest that all unusual appearances in this region should be investigated with the possibility of aneurysmal dilatation or rupture in mind. With modern techniques, particularly angiocardiography, it should be possible, in known cases of coarctation, to detect the earliest evidence of dilatation or rupture of the aorta.

With the advent of surgical treatment as an established procedure in suitable cases of coarctation, the diagnosis, prognosis, and treatment of infective lesions of the aorta became of greater importance. If endarteritis is suspected or diagnosed before radiology reveals any significant degree of aortic dilatation, it is possible that early intensive treatment may effect a cure and prevent such severe damage to the aorta as to preclude surgical measures. Once an aneurysm has formed, it is still possible that intensive therapy may completely heal the lesion, though the condition of the aorta may be

much less favourable for surgery. That this is possible is shown by a report of Nicholson (1940) where in a child of ten years, a mycotic aneurysm below the coarctation underwent spontaneous resolution and showed signs of calcification four years later. When rupture has occurred, even if minimal in extent, it is doubtful if treatment can do more than delay the course of events. Although the present case received adequate penicillin for the treatment of most cases of bacterial endocarditis in a child of four years, necropsy revealed that penicillin had had little effect upon the course of the disease.

Pathogenesis of Rupture in Coarctation of the Aorta. Abbott (1928) gives rupture of the aorta as the cause of death in 40 cases (20%) of her series of 200, and Reifenstein, Levine, and Gross (1947) in 24 cases (23·1%) of 104. In most of these the rupture has been in the ascending aorta. Up to 1946 only 16 cases of rupture distal to the stenosis had been reported, ten cases of so-called 'spontaneous' rupture, and six cases of rupture following mycotic endarteritis.

Table 1 is an analysis of the number of cases of rupture of the aorta reported (*a*) as spontaneous, and (*b*) as due to ruptured mycotic aneurysm.

Since Reifenstein's review two further cases of spontaneous rupture have been reported (Lenegré and de Brux, 1945).

Table 1 shows that rupture of the aorta distal to the coarctation is much less frequent than rupture proximal to it (16 cases of the former as against 56 of the latter in the combined series). It is to be noticed that there were only three cases of aortitis proximal to the coarctation, of which two ruptured. There were altogether 21 cases of aortitis distal to the coarctation occurring either alone or together with endocarditis, of which six had undergone rupture. In addition, there were ten cases of the rupture distal to the coarctation, which were classified by Abbott and Reifenstein as 'spontaneous.' However, a review of the cases so classified suggests that this may be misleading.

It does not seem surprising that rupture should occur in the ascending aorta. The increased blood pressure developing in this region would be expected to lead to secondary effects: dilatation of the ascending aorta and atheroma, with weakening of the wall and degeneration of the media. In the majority of cases of rupture these changes are present. Microscopically, the media shows thinning, with a decrease and interruption in the elastic tissue, increase in connective tissue and hyaline and fatty change. These changes may, however, be due in part to a congenital defect of the media (Turnbull, 1915; Abbott, 1928). Any sudden increase of pressure in the aorta, acting at the site of election just above the aortic cusps, might cause a tear. It is significant that in most of these cases a dissecting aneurysm is first formed, followed at an interval of some hours or days by its rupture.

It is not so obvious, however, why rupture should occur distal to the coarctation. The increase of pressure which may modify the structure of the ascending aorta is absent beyond the stenosis, so that similar degenerative changes are less likely to be produced. If the congenital defect be a predisposing cause, it is difficult to understand why the rupture should not have occurred in the ascending aorta, since this defect of the media is general and it is in this region that the wall is subjected to a considerably greater strain. Atheroma of the descending aorta with or without medial degeneration is a frequent finding in the older subject, independently of the presence of the coarctation. If either of these causes operated, it would be expected that in most cases a dissecting aneurysm would be formed, and it is perhaps significant that in the man aged 62 years with rupture some distance below the stenosis (Hecker, 1939), this did, in fact, occur.

A third predisposing cause may be destruction by infection of muscular and elastic tissue of the aorta. Such a process may involve the media either by the lodgement of infected emboli in the vasa vasorum or by extension from an infective endarteritis of the aorta. The former was suggested by Narr and Johnson (1934) to explain rupture of the ascending aorta in their case of a boy aged seven years. When infection of the aorta is present, it is almost invariably found immediately beyond the coarctation, and it is difficult to believe that an embolus would select such a limited area in which to settle. It is our view that this condition always begins with intimal involvement. For this to occur there must be some predisposing condition of the intima of the aorta which renders it susceptible to infection. Grant and his colleagues (1928) discovered small thrombi on the valves of the heart, especially where these were deformed by previous rheumatism or showed congenital anomalies. They considered that these thrombi formed a suitable foothold for circulating bacteria. More recently, Duguid (1948) has showed that similar thrombi are commonly found on the intimal surface of the aorta. Should these arise immediately beyond the coarctation where the blood flow must be considerably reduced and may be altered in direction, they would form a suitable nidus for the growth of organisms. The resultant weakening of the wall may be followed either by the formation of a saccular aneurysm or

TABLE 1
INCIDENCE OF RUPTURE OF AORTA AND AORTITIS IN COARCTATION OF AORTA OF ADULT TYPE

Author	Total No. of Cases of Coarctation	Proximal to Coarctation			Distal to Coarctation			
		Total No. of Cases of Rupture	Aortitis and Rupture	Aortitis without Rupture	Total No. of Cases of Rupture	Spontaneous Rupture	Aortitis and Rupture	Aortitis without Rupture
Abbott	200	36	1	0	8	3	5	8
Reifenstein	103*	20	1	1	8	7	1	7
		56	2	1	16	10	6	15

* One case (Evans, 1933) is cited in Reifenstein's series, and is quoted also in Abbott's series (Turnbull, 1915).

rupture into the mediastinum and a false aneurysm. The infection may spread to neighbouring tissues or pressure may lead to atrophy with final rupture of the aneurysm into such structures as the bronchus, oesophagus, and pleural sac. This sequence of events is to some extent borne out by a study of the reported cases of aortitis without ruptures. Some authors record friable vegetations only (Babington, 1847; Kretz, 1895; Mackenzie, 1927; de la Chapelle and Graef, 1931; Walker and Livingstone, 1938). Focken (1924) found ulceration in addition to vegetations in both his cases; Fawcett (1905) and Poynton and Sheldon (1928) found definite bulging of the aorta. Saccular aneurysms were present in the cases reported by Kellog and Biskind (1934) and by Bauer and Iverson (1945). In our case, it is almost certain that infection began on the intima of the aorta, a false aneurysm was produced, and the wall of the oesophagus was finally eroded with a subsequent fatal haemorrhage.

It is probable that the presence of an established infection of the aortic valve will predispose to aortitis. Of ten cases of aortitis in Reifenstein's series (table 1), four had aortic endocarditis, whereas of 93 cases of coarctation without aortitis in the same series, only 11 had aortic endocarditis.

It is interesting to note that in spontaneous rupture of the aorta due to accident injuries, the site of the tear has frequently been observed (Tannenbaum and Ferguson, 1948) as just above the aortic cusps and just distal to the attachment of the ligamentum arteriosum. Direct experiment has shown (Oppenheim, 1918) that at a pressure of 3,000 mm. Hg, the normal aorta will sustain rupture at one or other of these sites. These positions are points at which the aorta is relatively fixed, one by the heart and the other by the ligamentum arteriosum which is attached to the structures at the root of the lung. These correspond to the usual sites of rupture in coarctation of the aorta. It appears probable that when the wall of the aorta is weakened at either of these points an increase of arterial pressure, which would be without effect on the normal vessel, is sufficient to rupture a diseased artery.

Eighteen Cases of Rupture Distal to Coarctation. In an attempt to evaluate the part played by high blood pressure, congenital defect of the media, and infection, a review of reported cases of rupture of the aorta distal to the coarctation was made. Table 2 shows the relevant details of the 18 cases of rupture. One other case of rupture (Bargi, 1934) distal to the coarctation has been reported, but as the original communication is not available it has not been included.

SEX AND AGE. As in coarctation of the aorta generally, there is in this series a much larger proportion of males than females (approximately four to one). The average age of death from rupture distal to the aorta, when the rupture followed aortitis, was 17·3 years, whereas when the rupture was spontaneous, it was 37 years. The significant difference in the average age at death in these two groups seems to support the conclusion that the cause of the rupture in each type of case is different. This may be compared with the average age at death of 33·5 years in Abbott's 200 cases, and 35·0 years in Reifenstein's series. It is interesting to note that the average age at death of 13 cases of aortitis distal to the coarctation without rupture was 20 years. It would be expected that in rupture due to medial degeneration the average age would be higher than in rupture following aortitis, as this group would include a certain number of cases of atheroma, in which the degeneration was unrelated to the coarctation.

BICUSPID VALVES. The condition of the aortic valve was mentioned in only ten cases, in four of which they were said to be bicuspid. If it is assumed that this anomaly was not present in those five cases where the condition of the valve was not mentioned, the incidence of bicuspid valves in this

TABLE 2: RUPTURE

Group A. 17 *Years of Age and Under* (*seven cases*)

Author	Sex and Age (in Years)	Bicuspid Aortic Valve	Ascending Aorta	Descending Rupture
Present authors	Male 4	+	Slight atheroma	Rupture of false aneurysm
Smith and Targett (1897)	Male 9			Rupture of aorta formed a false aneurysm
Reifenstein's Case 2 (1924)	Male 10½		Slight dilatation	Dilatation and rupture forming a false aneurysm
Moragues *et al.* (1942)	Male 11	−		Rupture of saccular aneurysm
Libman (1928)	Female 12			Rupture of mycotic aneurysm
Goodson (1937)	Male 16½	+	Normal	Rupture of saccular aneurysm
Smith and Hansmann (1926)	Male 17	+	Atheroma	Rupture forming false aneurysm

Group B. Over 17 *Years of Age* (11 *cases*)

Barsantini and Bozzano (1938)	Male 24	+	Slight dilatation Marked atheroma	Large tear of aorta
Lenegré and de Brux's Case 1 (1945)	Male 24			Rupture of dissecting aneurysm
Zaslow and Krasnoff (1943)	Male 25	−	Normal	Rupture of dilated aorta well beyond constriction
Mönckeberg (1907)	Female 26	−	Hypoplasia of arch	Rupture of loculated pocket at site of insertion of ductus
Beneke (1922)	Male 28	−	Slight dilatation	Rupture of aneurysm with many large vegetations
Leudet (1858)	Female 37	−	Normal	Rupture of irregular saccular aneurysm showing atheroma
Koletsky (1942)	Male 38			Rupture of saccular aneurysm which showed large friable vegetations
Lenegré and de Brux, Case 2	Female 41			Rupture of saccular aneurysm
Carney Hospital Records (1947)	Male 45			Rupture of aorta forming dissecting aneurysm
Kriegk (1878)	Male 48	−		One tear above and another below leading into dissecting aneurysm
Hecker (1939)	Male 62			Tear of dilated aorta 6 in. below constriction, forming dissecting aneurysm

RUPTURE DISTAL TO COARCTATION

escending	Aorta				
	Microscopy	Organism	Degree of Coarctation	Remarks
	Near tear: Infective endarteritis	Staphylococcus	Extreme	Rupture of mycotic aneurysm
aneurysm	Rupture of intima and media		Extreme	Probably rupture of mycotic aneurysm, since there were inflammatory adhesions around it.
g a false	Necrosis of wall of aorta with abscess formation	Pneumococcus	Extreme	Rupture of mycotic aneurysm
	Vegetations showed inflammatory cells. Wall infiltrated by inflammatory cells.	None seen	Extreme	Probably rupture of mycotic aneurysm
		Strep. anhaemolyticus		Rupture of mycotic aneurysm. 'Chills and Sweats' five weeks before death
	Aorta small and thin walled below aneurysm otherwise normal		Extreme	Signs of severe infection for three months before death. Splenic and renal infarcts present. Rupture of mycotic aneurysm
n	Aorta near aneurysm normal	*Strep. viridans*	Moderate	Bacterial endocarditis of aortic and mitral valves. Rupture of mycotic aneurysm

			Extreme	Probably spontaneous rupture
n	No medial degeneration. Endarteritis obliterus of vasa vasorum		Moderate	Spontaneous rupture
ll beyond	Mucinous degeneration of media. No evidence of syphilis or atheroma		Moderate	Spontaneous rupture
at site of			Extreme	Spontaneous rupture due to traction by ligamentum arteriosum. No evidence of infection microscopically
any large		*Strep. viridans*	Extreme	Rupture of mycotic aneurysm. Died cerebral haemorrhage. Strongly positive Wassermann reaction. Mitral and aortic endocarditis
aneurysm			Extreme	Spontaneous rupture due to atheroma
m which	Marked thinning and interruption of elastica. Infiltration with polymorphs	*Haem. staph. albus*		Rupture of mycotic aneurysm
	Medial necrosis and fibrosis of aorta. Vasa vasorum partly obliterated. No definite evidence of syphilis		'Slightly narrowed'	Spontaneous rupture. Possibly syphilitic in origin. (Strongly positive Wassermann reaction)
dissecting			Moderate	Spontaneous rupture. Death from congestive cardiac failure 18 months after rupture
ow leading			Moderate	Spontaneous rupture possibly produced by kinking due to traction by ligamentum arteriosum
elow con-urysm			Extreme	Spontaneous rupture. Death by suicide

series was 22·2%. Abbott (1928) reports the incidence as 23·5% and Reifenstein (1947) as 42·3%. The high incidence of bicuspid valves will obviously predispose to bacterial endocarditis, and as has been shown above, to aortitis.

DEGREE OF STENOSIS. According to Abbott's classification of moderate, extreme, and complete stenosis, there were six cases of moderate, and ten of extreme stenosis whilst there were no cases of complete atresia. Abbott (1928) found seven cases of moderate and 15 of extreme stenosis, and 11 of complete atresia in 33 cases of rupture of the ascending aorta. There seems to be no adequate explanation for the absence of rupture distal to the coarctation in cases of complete atresia.

AORTA. In nine cases where the ascending aorta was mentioned there was atheroma in three cases, and it was stated to be absent in two. There was slight dilatation of the ascending aorta in two instances, hypoplasia in one, and it was of normal size in four cases. Similarly the descending aorta appeared to show no atheroma in most cases and this would indicate that atheroma played no significant part in the aetiology of the ruptures. There was dilatation of the descending aorta in six cases, with the formation of a fusiform or a saccular aneurysm not obviously due to endarteritis.

SITE AND CHARACTER OF TEAR. In two instances an aneurysm was possibly first formed by the traction of the ligamentum arteriosum at its insertion into the wall of the aorta and this aneurysm had then ruptured. In four other cases, a dissecting aneurysm had formed, in one of which it was situated 6 in. below the coarctation in the descending aorta. In six cases, mycotic aneurysms were definitely stated to be present and these had ruptured. In three instances a saccular aneurysm, the wall of which was formed in the most part by blood clot, had ruptured. In two of these inflammatory adhesions or vegetations were also of mycotic origin. In all but two cases, the tear was just below the coarctation, which has been shown to be one of the sites of election for rupture and is, moreover, the commonest site of endarteritis in coarctation.

MYCOTIC ENDARTERITIS. In five cases the cause of death was stated to be a rupture of a mycotic aneurysm, and in each of these, the causative organism was identified; it was different in each case. In one other case of rupture of mycotic aneurysm from which *Strep. viridans* was isolated, death was due to cerebral haemorrhage. That mycotic endarteritis was present in three other cases is probable, since in two cases vegetations or adhesions were observed, and in the last case tonsillectomy (for chronic tonsillitis) had been performed ten days previously, and at necropsy splenic and renal infarcts were found.

A consideration of these cases supports the conclusion that rupture of the aorta distal to the coarctation appears in many cases to be different in origin from rupture proximal to the aorta. Mycotic endarteritis is very rare in the latter, and rupture is almost always due to the wall of the aorta being weakened by the effects of high blood pressure. In the former, mycotic endarteritis is present in 50% of the cases with resultant weakening of the aorta and rupture. This occurred in the younger age group. In the remainder, the reason for the rupture is more obscure. Congenital defect of the media may be a factor, and, although atheroma was not mentioned in the majority of cases, it might well be assumed that some degree of atheroma was present, especially as the average age of this group was much higher than in the group of mycotic endarteritis.

Summary

A case of rupture of the aorta distal to coarctation in a boy aged four years is reported.

The clinical findings and pathogenesis of rupture of the aorta distal to coarctation are discussed and all the cases previously reported are reviewed.

The importance of the prevention of endarteritis, and of its early diagnosis and treatment in such cases is emphasized.

It is concluded that of the three predisposing factors, mycotic endarteritis plays a much greater part in the aetiology of rupture distal to the coarctation than in rupture of the ascending aorta proximal to it.

We wish to thank Dr. N. M. Jacoby for permission to publish the case, Dr. C. J. C. Hodson for criticism of the section on radiological findings, Dr. H. H. M. Mackay for her help and criticism, Dr. Elsie Gibbons for her careful clinical notes, and the Southern Group Laboratory for the photographs.

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CHRONIC CARDITIS IN A CHILD OF NINETEEN MONTHS

BY

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(RECEIVED FOR PUBLICATION, JUNE 22, 1949)

Chronic carditis in infancy is so rare that the following case, which presented both clinical and pathological problems, is considered worth reporting.

Case History

A.N., a boy and the only child, was stated to have been a fortnight premature and to have weighed 5½ lb. at birth. Breast fed for one month, he was then given bottle feeds as his mother had insufficient milk. On this he thrived, and subsequent progress was normal with no history of any illness until his last. At 16 months he weighed 21 lb., and at 18 months he had 12 teeth and could walk and speak a few words. Both parents were healthy, and there was no history of illness during the mother's pregnancy.

Three weeks before admission, at the age of 19 months, the child became fractious and appeared unwell. The only abnormal physical sign was stiff and painful middle fingers, but the general condition deteriorated and he was eventually sent to hospital.

Clinical Examination. On admission the child was lying quietly, but resented disturbances. The cheeks and mucous membranes were pale, the limbs hypotonic, and the nails spoon-shaped. There was sweating and apparent recent loss of weight, the actual weight being 18 lb. 3 oz. The skull circumference was 19½ in. (normal average at this age, 18 in.), and the anterior fontanelle admitted a finger tip, indicating delay in closing, which is normally complete at 18 months. The middle finger of each hand was semi-flexed and painful and slight oedema of the feet and lumbar region was noticed.

The temperature was 99° F., respiration 40, and pulse 135 per minute. The blood pressure was 75/40. Scattered râles were noted.

The apex beat was not localized on palpation, but on percussion the area of cardiac dullness extended three finger breadths to the left of the sternum in the fourth intercostal space and one finger breadth to the right in the third space. On auscultation a blowing apical systolic murmur, conducted into the axilla, was heard. A systolic murmur was also audible to the right of the sternum.

The liver was palpable two finger breadths below the costal margin and the spleen one finger breadth.

Special Investigations. Radiographs showed an enlarged heart and some opacity of the left upper and lower zones in the chest. The fingers appeared normal.

The Mantoux reaction (1 : 10,000) and the tuberculin patch and jelly tests were negative.

BLOOD EXAMINATION. R.B.C. 4,200,000/cu. mm.; Hb 72% (Haldane). The film showed mild anisocytosis and slight hypochromia. W.B.C. 12,200 (neutrophils, 52%; eosinophils, 1%; lymphocytes, 42%; monocytes, 5%).

Progress. For the first three days after admission there was little change in the child's condition, but the fourth day brought the onset of marked dyspnoea and cyanosis. An oxygen tent gave slight relief of symptoms, but penicillin and sulphathiazole in ordinary doses were without effect, and the clinical course was rapidly downhill with increasing dyspnoea, cyanosis, and sweating. Death occurred on the ninth day with great respiratory distress.

No clinical diagnosis had been made. The possibility of rickets, tuberculosis, or a pyogenic infection had been dismissed after the special investigations.

Post-mortem Findings

Necropsy was performed 9½ hours after death.

The body showed little subcutaneous fat. Each pleural cavity contained about 100 ml. of straw-coloured fluid with no clot. The pericardium appeared normal.

The heart (Fig. 1) weighed 65 g. (normal at this age is 52 g.). On section the right ventricle measured 4·5 mm. in thickness and the left ventricle 11 mm. The striking feature was the great thickening of the endocardium. Both mitral and tricuspid valves felt like cartilage, and the chordae were short, thick and fused. At the bases of these valves fibrosis could be seen extending into the

myocardium, and in other areas of the muscle small patches of fibrosis were evident, particularly at the bases of the papillary muscles.

The contiguous margins of the cusps of the aortic valve were fused, while the free margins were thick and hard. The adjacent aortic wall was also thickened, and at a distance of 2 cm. above the valve measured approximately 2 mm. in thickness. Above the valve the lumen of the aorta appeared normal throughout, while the intimal surface was quite smooth.

Both lungs showed marked chronic venous congestion. The costo-chondral junctions and middle fingers were normal on section and no abnormality was found in any other organ or tissue.

Histology. Sections were taken from both right and left sides of the heart to show the auriculo-ventricular junction and the attachment and cusp of the appropriate valve. The section from the left side included the circumflex branch of the left coronary artery. The histological picture in each section was similar. The epicardium appeared normal. The myocardium showed areas of fibrosis adjacent to the blood vessels. There was also marked fibrosis at the base of the valve, the fibrous tissue interlacing with the muscle at this point. The circumflex branch of the left coronary artery showed subintimal fibrosis, very marked replacement fibrosis of its medial coat, and also paravascular fibrosis. The valves were both thick and consisted of hyaline fibrous tissue. No vegetation and no signs of acute or subacute inflammation were evident.

The intima of the aorta was normal (Fig. 2). The media was normal at its inner part, but near the adventitial junction had been involved in a severe inflammatory process. Fibrosis was marked adjacent to the vasa vasorum and in many places islets of elastic tissue were surrounded by fibrous tissue, as if cut off by an advancing tide. The adventitia was irregularly thickened and consisted of hyaline scar tissue.

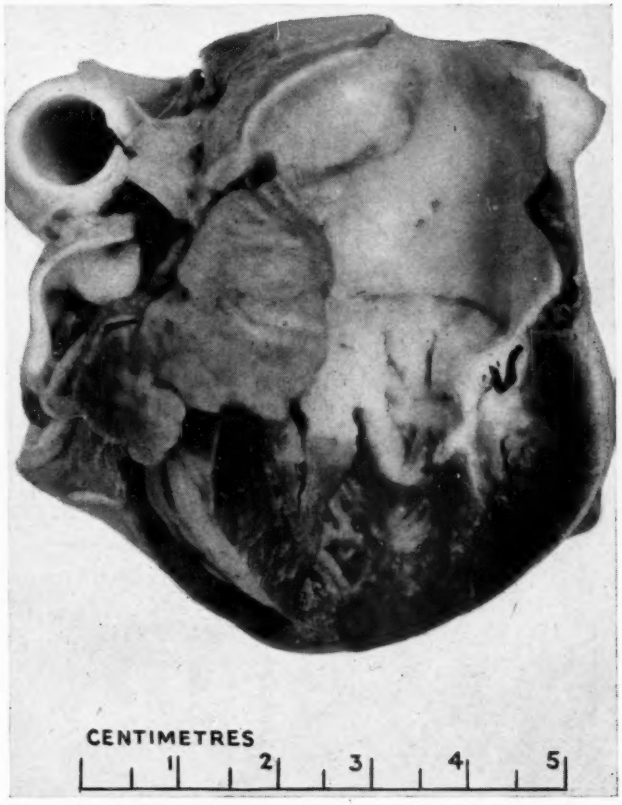

FIG. 1.—Heart showing mitral valve and aorta.

Discussion

The problem here was to ascertain the nature and age of the lesion, which for practical purposes was confined to the heart and aorta. The picture of myocardial fibrosis, valvular distortion and thickening with fusion of chordae tendineae, is so highly suggestive of a chronic rheumatic process that it is hard to see what alternative diagnosis could be made. The only logical possibility is an endocarditis, not rheumatic, of unknown aetiology, and as yet not clearly defined. Verrucose endocarditis due to disseminated lupus erythematosis does not meet the case as no abnormality was found in any other organ, nor did the clinical picture in any way suggest the disease. Fiedler's myocarditis spares the endocardium, which in this case was the most heavily damaged part. So-called idiopathic cardiac hypertrophy is an improperly understood condition. The literature on the subject was reviewed by Kugel and Stoloff in 1932 and again by Kugel in 1939. While the clinical picture they describe is similar to that in this case, the endocardium is only slightly, if at all, involved. Moreover, a congenital lesion cannot be considered as the picture is so obviously that of a chronic healed inflammatory process.

If rheumatic carditis is to be considered, then an acute rheumatic process is implied, which is very rare in infants.

Paul White (1944) states that 'rheumatic heart disease . . . is especially rare before the age of two years'. Various writers have described the disease however. In 1896 Abrahams reported six cases in new-born infants whose mothers were suffering from rheumatic fever while in labour. The infants all had arthritic signs or cardiac murmurs, the

signs and symptoms responding to salicylates (but no follow-up of the patients is reported). Cathala and others (1936) described a child of 22 months with limb pains, an apical systolic murmur, and enlargement of the heart. The symptoms responded to salicylates, but the murmur remained and was considered to indicate mitral incompetence. Saubidet (1936) described three infants of 8, 18, and 21 months who showed joint pains and fever, but no abnormal cardiac signs; the symptoms responded to salicylates. These cases cannot be regarded as proven, although Cathala's patient showed a clinical course strongly resembling that of rheumatic carditis. Denzer, however (1924), reported three cases of infants under two years in which the diagnosis of rheumatic carditis was proven at necropsy. Two of these cases were acute, while the third was estimated at six months' duration.

Kissane and Koons (1933) described a case in which a woman was ill during pregnancy with rheumatic fever. The child was born with arthritis and cardiac murmurs and remained under the observation of the one physician until he was nine years old when he died in an attack of acute rheumatic fever. Necropsy showed chronic rheumatic carditis with a recent acute exacerbation.

Fischer (1934) described an infant one year of age dying with pneumonia. A clinical diagnosis of congenital heart disease was disproved at necropsy when rheumatic carditis, affecting mainly the mitral valve, was found.

McIntosh and Wood (1935) reviewed 24 cases in infants or young children in the New York Babies' Hospital. In six of these the diagnosis was confirmed at necropsy, the youngest child being 20 months old at death and suffering from acute rheumatism at the time.

There is, therefore, sufficient precedent to consider a diagnosis of rheumatic carditis in a child of 19 months. Having made this decision the next problem is to attempt to assess the age of the lesion. The recent work of McKeown (1945) on the evolution of the Aschoff nodule has shown that healing takes some nine months and that before this the lesions have a characteristic architecture and can be recognized as specific entities. When healing is complete there is simply scar tissue with no specific architecture, although the paravascular and subendocardial distribution is highly suggestive, as it was in this case. On these grounds it is suggested that this child had acute rheumatism early in its first year of life.

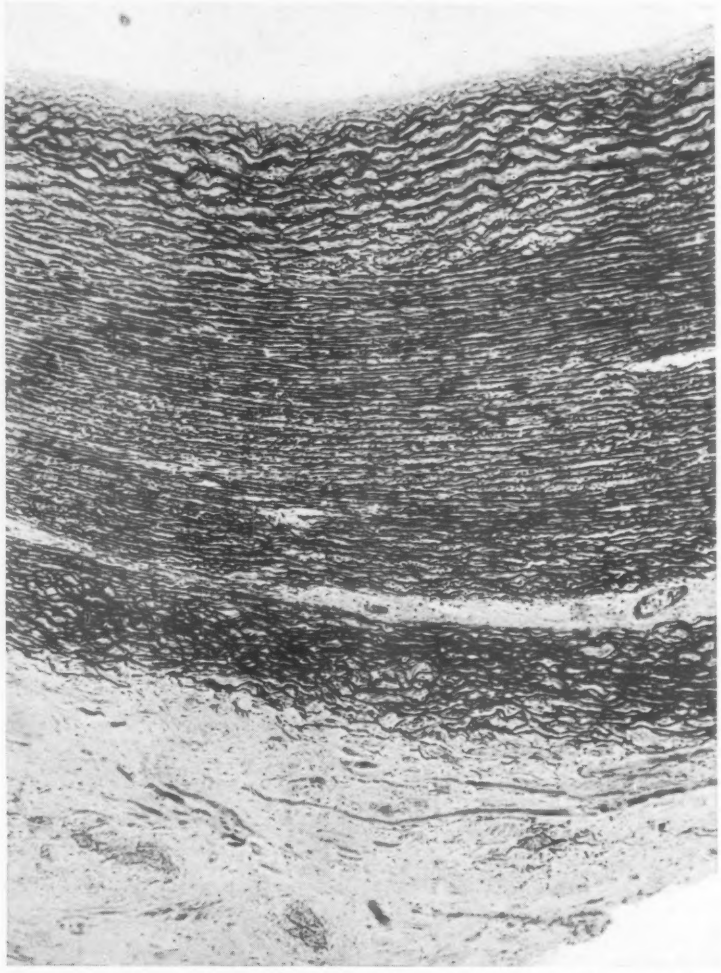

FIG. 2.—Transverse section of aorta × 75. Verhoff's stain for elastic tissue.

Summary

A case is reported of a child dying at the age of 19 months in which necropsy revealed a cardiac lesion suggestive of chronic rheumatic carditis.

I wish to express my thanks to Dr. Beryl Corner, under whose care this child was at the Bristol Children's

Hospital; also to Professors T. F. Hewer and C. Bruce Perry for helpful criticism and advice. My thanks are also due to Mr. G. W. Griffin and Mr. G. Rogers of the Department of Pathology, Bristol University, for the histology and photographs.

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TETANUS NEONATORUM

BY

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(Received for Publication, September 19, 1949)

Tetanus neonatorum has become a rare disease in civilized communities. That this is dependent on a general acceptance of basic elementary hygiene is emphasized by the record of the following 25 cases, all of whom were seen in the paediatric wards of University College, Ibadan, in the first six months of last year.

Ecological Background

Ibadan is a huge, sprawling town in western Nigeria. There is a fluid indigenous population of some 500,000 people. Most are of the Yoruba tribe, with a minority of Hausa and Ibo. Housing is primitive and overcrowding the rule. The vast majority have little or no education, and certainly no conception of even the simplest hygiene. During the dry season the town is covered with ironstone dust, and goats, which are commonly kept, wander all over the town, both inside and outside the houses.

Treatment of the Umbilicus

All cases in this series were Yorubas, with the exception of one patient, E.B., who was of the Benin tribe.

In this series the cord was cut at birth, a sharp splinter of palm wood or a piece of broken bottle being used. The cord is usually tied with a piece of thread or string. Various dressings seem to be used, most usually ghee butter, but occasionally palm oil, or a mixture of salt and the crushed-up central pith of the tagiri fruit, or gin and palm oil. A piece of rag heated by being placed on hot stones by the fire usually completes the dressing, which may be renewed at irregular intervals. As a result of this regime all grades of umbilical infection are common, umbilical abscesses and septicaemia being not infrequent. It is, therefore, not surprising that spores of *Cl. tetani* are often introduced into the wound from the goat-soiled dust.

Mode of Onset

The incubation period varied from five to ten days. It was six days in 64% (16 cases).

There was no history of an abnormal or difficult labour. All cases were confined in their own homes.

In every case the earliest feature noticed by the mother was the child's inability to suck the breast. This was followed after about 24 hours by definite and increasingly frequent extensor spasms. Constipation and continuous crying were part of the initial picture noticed by many of the mothers.

Clinical Picture

When once developed the clinical picture was characteristic. The children were usually well-nourished. The umbilicus was clinically infected in most cases (88%), a blackish eschar being not infrequent. The child's resting posture usually showed a moderate ' risus sardonicus,' with the eyes held closed, slight hypertension of the spine, the arms semiflexed at the elbows, the hands clenched, the legs semi-flexed at the knees (Fig. 1). Tetanic spasms were superimposed upon this background. These were produced by a considerable increase in the hypertonus seen in the resting posture (i.e. marked risus, the arms held rigidly in semiflexion, hands tightly clenched, often with the thumb inside the hand, and the back hyperextended, but always to a less degree than in an adult case). There was at the same time spasm and rigidity of the muscles of the anterior abdominal wall, adductor spasm of the thighs, dorsi-flexion of the feet, and severe plantar flexion of the toes. This last was a very marked feature. Spasms occurred in most cases about every five minutes (varying from every second to every quarter of an hour), becoming more frequent as the illness developed.

Treatment

Treatment had to be based on the limited range of drugs available. Anti-tetanus serum (20,000 units i.m.) was given in all cases. Expressed breast milk was given by spoon or pipette. Subcutaneous saline was used in almost all cases. An attempt was made to nurse the children in a quiet corner of the ward, but the mothers were usually unable to understand the importance of this and carried

the babies about on their backs in the usual Yoruba fashion.

The most usual hypnotic was paraldehyde which was given intramuscularly in doses of 2-4 ml. four-hourly. Immediate results were quite good, the children having less frequent fits and being much quieter during the period of paraldehyde sedation. In two cases the intramuscular paraldehyde produced chemical abscesses of the buttocks. Alternatively chloral hydrate was used, either by mouth (gr. 3-5 four-hourly) or rectally.

Results

The results with this treatment were very bad. Seventeen cases died in the first 36 hours of treatment (68%), six lived for three to five days, one lived for 42 days, and one case recovered. The most usual course in an average case was for the spasms to become rapidly increasingly frequent. Fever (100-105° F.) and tachycardia were the rule. An analysis of the causes of death is tabulated below.

ANALYSIS OF CAUSES OF DEATH IN PRESENT SERIES

Cause of Death	No. of Cases	Percentage of Cases
No obvious cause	18	72
Hyperpyrexia	2	8
Cardiac failure:	2	8
1, acute ventricular		
1, generalized congestive		
Bronchopneumonia ..	1	
Anaemia and inanition ..	1	

Case Report

E.B., a female infant of the Benin tribe, aged nine days, was admitted to Jericho General Hospital, Ibadan, on April 4, 1949. There was a history of a normal uncomplicated delivery at home. The umbilicus had been cut and tied in the usual way. It had been dressed with hot rags and a gin and palm oil mixture. The mother had noticed that the child had been costive for two days and had not been able to suck the breast since the day before admission. On examination the infant showed risus sardonicus, the neck slightly extended, the arms held stiffly in semiflexion with hands clenched, and the toes plantar flexed (Fig. 1). Spasms recurred every minute or so. The umbilicus was moderately infected, with slight herniation. Temperature was 101° F.

The infant was given anti-tetanus serum, 20,000 units i.m. and paraldehyde 2 ml. four-hourly, and expressed breast milk 3 oz. four-hourly.

8.4.49. Spasms almost kept under control by paraldehyde.

9.4.49. Blackish areas appearing on both buttocks. Paraldehyde discontinued. Started on oral chloral hydrate gr. 3 four-hourly.

11.4.49. Obvious sloughing, necrotic areas on both buttocks.

12.4.49. Spasms almost controlled by chloral. Abscess cavity has appeared in each buttock. Rather dehydrated, put on subcutaneous saline (5 oz. four-hourly).

20.4.49. Condition still much as before, but vomiting milk. Losing weight rapidly. Clean, but indolent, abscess cavities in both buttocks.

FIG. 1.—The infant described in the case report.

30.4.49. Occasional spasm only. Becoming anaemic (Hb 50%).

3.5.49. Considerable deterioration in condition. Bluish. Feeble. Dehydrated. Slight abdominal distension.

5.5.49. Vomiting occasionally.

12.5.49. No spasms. Taking milk quite well with a spoon. Occasional vomiting only. Cries well. Very dehydrated and emaciated. Buccal pad very prominent. No risus. Slight stiffness of the arms, held in slight flexion. Hands still firmly clenched. Umbilical hernia more prominent. Ulcers on buttocks clean but not

healing. Has had persistent fever of about 99-100° F. since admission.

13.5.49. Has developed oedema of scalp, with definite pitting on pressure. Urine shows no albumin.

15.5.49. Oedema has extended from scalp to face, head and neck. Unable to see eyes because of facial oedema. Rounded tumour 5 cm. in diameter has appeared above the inner end of the right clavicle. It is expansile on crying or during a spasm, can be reduced from above downwards into the thorax behind the right clavicle, and appears to contain air.

16.5.49. Oedema worse. Dyspnoeic. Tachycardia (150/min. irregular). Died in afternoon.

During the last two weeks of the illness, the child was treated with intramuscular liver injections, oral ferrous sulphate, cod liver oil, and ascorbic acid.

This patient seemed to be recovering from the tetanic spasms, but died of inanition and anaemia. The interesting feature of the case was the development of an air-filled tumour in the right side of the neck. This was almost certainly an aerocoele, arising from either the lung or a large bronchus. Presumably the constant strain of the tetanic spasms repeated over weeks, combined with anaemia, vitamin deficiency, and inanition, had produced a stress hernia, which had caused pressure on the superior mediastinum, and resultant oedema of the head and neck.

Tetanus neonatorum is a comparatively common disease in Ibadan during the dry, dusty season. It should be completely avoidable if simple hygiene is practised. The majority of cases are fulminating so that it is unlikely that any treatment would be of use, although the possibility of using 'Flaxedil' (Tri-(diethaminoethoxy) benzene—triethiodide) intravenously via the anterior fontanelle must be considered.

Summary

The aetiology and clinical picture of tetanus neonatorum in Ibadan, Nigeria, is illustrated by a brief review of 25 cases. An unusual case of chronic tetanus neonatorum, complicated by anaemia, inanition, and an aerocoele, is described.

I should like to thank Professor A. Brown, of the Department of Medicine, University College, Ibadan, for permission to publish this paper.

THE SOCIAL BACKGROUND OF INFANCY: THE DOMESTIC ENVIRONMENT OF 471 OXFORD BABIES

BY

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From the Institute of Social Medicine, Oxford

(RECEIVED FOR PUBLICATION, AUGUST 22, 1949)

It is generally recognized that infant mortality is a sensitive index of social conditions, showing high rates where bad housing, overcrowding, and maternal neglect prevail. Although there has been an appreciable reduction in the rate in England and Wales which, 50 years ago, was 150 per 1,000 births, and is now less than 50, nevertheless the data available still indicate wide variations in the mortality in infancy, not only in different towns but also in different socio-economic groups. It is very probable that side by side with the disparities revealed by mortality statistics similar variations obtain in the growth and health of babies living under different social and environmental conditions.

Although the last century has witnessed vast social improvements, Chadwick's 'Report on the Sanitary Condition of the Labouring Population of Great Britain' (1842) still illustrates the factors which to-day have to be considered in preparing the social records of children in an enquiry such as the Oxford Child Health Survey.

The Oxford Child Health Survey

This survey was referred to in the Annual Report (1945) of the Institute of Social Medicine as an investigation which 'has been undertaken with a view to studying and comparing the health, development, and sickness experience of children in all social groups from the first weeks in life to the age of five years. The clinical and somatometric examinations are made at three-monthly intervals. At six-monthly intervals (from the age of six months) radiographic studies of skeletal development are included. As far as possible, both major and minor sickness episodes are also recorded. Parallel social, domestic, and economic studies are made in the course of regular home visits.'

Source and Nature of Data. The present paper is concerned with social studies only and should be considered against a picture of Oxford as a whole, such as is given in the 'Survey of the Social Services in the Oxford District' by the Barnett House Survey Committee (1938 and 1940). Oxford consists of a central university and shopping area; a large northern residential area; a large southern area where a high proportion of workers at Morris Motors and the Pressed Steel Company Limited (employing about 15,000 workers between them) are housed; and some slum areas near the stations and the canal.

The children, whose circumstances are here under review were born between 1944 and 1947, and were enrolled, under the age of six weeks, at eight of the ten infant welfare centres in Oxford and at the Oxford Mothercraft Clinic (a private clinic). The health visitors explained the purpose of the survey to the mothers who anticipated living in Oxford for the following five years, and those who wished to do so enrolled on a voluntary basis. There was thus a measure of selection in that only those mothers who were interested enough to attend welfare centres were drawn upon at this stage. Nevertheless, all social classes are represented.

After enrolment the children were immediately examined medically and measured by the paediatrician. Then the medical-social worker, who had been present at the interview, asked the mother if she might visit her to learn further particulars relevant to the home situation and the baby's health.

Home Visiting Technique. Although the purpose of home visits in a survey of this kind is to accumulate specific information, every effort was made to give an air of informality to the interviews. As far as possible the mothers were encouraged to talk without prompting; where questions were needed, attempts were made to follow a natural thought-sequence and leading questions were avoided. At the first visit the purpose of the Survey was again discussed in order to clear up any doubts or misunderstandings.

In practice, information was then usually gleaned in the following order. First, the child's diet was discussed and, if he was not breast-fed, possible reasons for the mother's failure were considered. This led naturally to consideration of the mother's present health, her health during pregnancy and her own past history and family history, and so to her date of birth, her husband's date of birth, and the date of marriage. The husband's occupation was noted in order to assign the family to one of the Registrar-General's five social classes.

After explaining that we were interested to see whether the density of the household had any bearing on the sickness rate, particulars of the number of persons in the house were noted and compared with the number of rooms. From this point details relating to bathrooms, W.C.s, laundry facilities, and other domestic conveniences were taken up in natural sequence. Gardens and allotments were then discussed in turn, and, in passing, the amount of fresh air secured for the baby, and how he was said to be sleeping, were recorded.

Essential details relating to feeding and dates were written down at the time, but other information was memorized and entered later in order to make the interview a chat rather than an interrogation. In particular, details to assist in assessing 'maternal efficiency' have been observed and grouped under the following five headings: (1) State of child; (2) state of home; (3) diet of child; (4) health of mother; (5) attitude of mother to child. Each of these was classified as 'good,' 'fair,' or 'poor,' and was checked at each of the subsequent six-monthly visits, which were without appointment. During the home visits an assessment was also made of the house, involving observations on age, state of repair, ventilation, light, damp, and whether or not condemned.

The second visit, at six months, had the special object of obtaining details of the early weaning history. At a year, details of diet were again noted and this was therefore an appropriate time to ask the mother if she could give an account of the amount of money she was spending on food for the family. Information has been very readily obtained.

As a result of these three home visits during the baby's first year of life, the following particulars were recorded and have been made the basis of the present analysis:

CHILD'S PERSONAL PARTICULARS: Name; sex; date of birth; address; clinic.

FAMILY PARTICULARS: Age of father; occupation of father; age of mother; occupation of mother; date of marriage; number in household; number of families in the house; number of adults in the house; number of children in the house; expenditure on food.

HOUSING PARTICULARS: Type of house; condition of house; number of rooms available for each household; number of rooms in the house; household conveniences.

The Family

Social Class. According to the statistics published by the Registrar-General, there is definite evidence that the infant mortality rate has varied markedly in the past between the social classes. Hence it was desirable to take into account the social stratification of the family from which each baby was enrolled.

The Registrar-General's five social classes are based on the occupation of the father, and are: Social Class I, higher professional grades; Social Class II, lower professional and administrative grades; Social Class III, skilled occupations; Social Class IV, semi-skilled occupations; Social Class V, unskilled occupations.

The number of babies in each social group is given in Table 1.

TABLE 1

DISTRIBUTION BY SOCIAL CLASS OF 471 OXFORD BABIES

Social Class	Number	Percentage
I	33	7·01
II	43	9·13
III	319	67·73
IV	43	9·13
V	33	7·01
Total	471	100

For convenience social classes I and II and social classes IV and V respectively have been considered together. It was purely fortuitous that the number in each of these two groups was the same.

It will be seen from Table 2 that Oxford has a higher proportion of social class III and a lower proportion of IV-V than the country as a whole. This is reflected in the recruitment of the Child Health Survey where there is a preponderance of social class III. Mothers from this class provide the bulk of the attendances at the City's welfare centres and, apart from this, are more likely to volunteer to join a survey and are less likely to default than mothers belonging to class IV-V. Babies representing classes I-II have mainly been drawn from the Oxford Mothercraft Clinic.

The fact that the social classes in the Child Health Survey are not in the same proportion as those in

TABLE 2

DISTRIBUTION BY SOCIAL CLASS

	Percentage in Each Social Class		
	I and II	III	IV and V
Population of England and Wales, Census 1931, Occupied Male ..	16·52	49·16	34·32
City of Oxford, 1931 ..	15·76	57·45	26·79
Child Health Survey, 1944–47	16·14	67·73	16·14

the country as a whole does not, of course, invalidate comparisons between the classes.

Unemployment among the fathers of the children in the survey has been negligible.

The Age of the Parents. The age of the father at the time of the birth of the baby included in the survey ranged from 20 to 57 years. The average showed little difference between the social classes, being 34 years in I-II, 33 years in III, and 35 years in IV-V. The average for the fathers in all the social classes was 33 years.

The age of the mother at the date of the birth of the survey child (which may or may not be her first child) ranged from 19-45 years, the range being slightly more limited in social class I-II. The average age in each of the three groups was 30 years. The distribution pattern of the age of the mothers in this survey approximately follows that for the whole country. There are, however, fewer mothers under the age of 25 in the survey. This may, in part, reflect the fact that in general a higher proportion of illegitimate babies is born to young mothers, and these babies were not fully represented in the survey. There were no mothers over the age of 50 in the survey.

Duration of Marriage. On the social records used, the day, month, and year of birth and of marriage have been entered, but only the year has been transcribed on to the punch-cards used for analysis. In social classes I-II the duration of marriage ranged from 1 to 16 years and the average duration at the birth of the 'survey baby' was 5·75 years. In social class III the duration ranged up to 25 years, the average duration being 6·73 years. Eight of the 319 mothers in this class were unmarried. In social classes IV-V the duration ranged up to 21 years and the average duration was 6·89 years. Three of the 76 mothers in this group were unmarried.

The proportion of unmarried mothers in the survey is therefore 11 in 471, or 2·3%, whereas in England and Wales as a whole the proportion of illegitimate maternities was 9·33% in 1945, and for births registered in Oxford in 1945 the figure was 8·75%. That there is a low representation of unmarried mothers in the survey is readily understandable, for the unmarried mother is more likely to go out to work and to lack the time to bring her baby for the examination required by the survey. In addition, a certain proportion of these children are cared for in institutions which are not covered by the survey, and a further number are adopted. There were only two adopted children.

Number of Surviving Children in the Family. Of the 471 families, 220 infants were only children at the time of enquiry, although not necessarily the firstborn as, in this instance, stillbirths and siblings who had not survived were not considered. There were two children in each of 143 families (including two families with twins in the survey); four to nine children in 45 families, and more than ten surviving children in three families. This follows closely the pattern of distribution by number of surviving previous children in England and Wales as a whole.

Occupation of the Mother. Of the mothers of the 471 children, 33 were at work before the child's first birthday. Of these 33, four were from social classes I-II, 12 from social class III, and 17 from social classes IV-V.

Twenty-five of these mothers were able to work without being separated from the child, either because the baby accompanied the mother to work (as was the case with the 11 mothers who did daily domestic work and the general practitioner who took her baby with her on her rounds), or because the mother lived and worked on the premises. Four of these mothers assisted relatives with shops: one of these was a fish-and-chip shop and three were small general stores. It was noteworthy on later enquiry into the children's feeding, that the children of the last three mothers 'didn't eat well' at meal times. It was soon discovered that they were in the habit of helping themselves to biscuits in the shop whenever they felt inclined.

Eight mothers had to leave their babies in the care of another person while they went out to work. One mother worked in a laundry when her baby was six months old, as her husband had lost several fingers in a factory accident. She left her son in the care of her own parents and her husband and, far from being neglected, the child was spoiled. The other seven mothers who had to go to work, leaving their children, were unmarried and all were working before the child was six months old. Five left the child with relatives, one with a foster

mother, and one took the child to a day nursery. There were four other unmarried mothers in this series. One worked as a resident domestic help, returning with her baby to her previous employer; one, who was living with the father of the baby, went out to domestic work, taking the child with her; one later married the father of the child. The remaining mother did not at first go out to work but stayed at home to look after the house whilst her own mother went out to work. She has since had a second illegitimate baby (her third pregnancy) for whom adoption has been arranged. Her first child (who is in the survey) now attends a day nursery while the mother works.

In this series only one child was taken to a day nursery before the age of one year. In any analysis of the subsequent social records of these children, a much higher number will be found to be attending day nurseries.

Housing and Amenities

The housing problem is too well known to require re-statement. Oxford, indeed, is fortunate in that not one of its houses was lost through enemy action, but, against this, is the fact that the population of Oxford has expanded rapidly. It is estimated that the population is more than double the 1901 figure of 49,000. In common with the rest of the country, building in Oxford was virtually at a standstill during the war years. In 'Oxford Replanned' (1948), Mr. Sharp has estimated that 'some 6,000 new dwellings are required in Oxford to meet the present and early needs of the people at present living or working in the city, without any consideration whatsoever of the possibility of future growth.'

Number of Family-Units Living in the House. For the purpose of this study, the family-unit has been taken to include only the following: (*a*) the survey baby, (*b*) the parent or parents, (*c*) the siblings, if any. The 'household' is the housekeeping unit in which the survey family-unit lives. For instance, if the survey family is living at the same address as the maternal grandparents, and the housekeeping arrangements and living rooms are communal, this establishment is classified as one 'household,' but two 'family-units.' Similarly, a friend or lodger who was catered for and was thus part of the one household would be considered as an extra family-unit. On these principles the number of family-units in the whole house has been recorded. It will be realized that multiple family-units do not necessarily indicate multiple 'households,' but it was felt to be of interest to note whether or not the survey family was living alone because of the possible implications in child management. For instance, the fact that there are others in the house may have some effect on how the baby sleeps.

During the three visits in the first year, the mother has been asked how the child sleeps, and at the age of one year an attempt has been made to assess this as 'good,' 'fair,' or 'poor.' This is an arbitrary value as it is necessarily based on the mother's statements, but the length of time the child sleeps during the day and at night was recorded, the mother's comments on the soundness of sleep or frequent waking at night being duly taken into consideration. It was noted that, of the mothers who stated that their children were not sleeping well, the majority (18% compared with 10%) were living where other people, apart from the immediate family, were occupants of the house. It can well be imagined that it is more difficult for a mother to break her child of bad sleeping habits when these have been aggravated by picking up the child each time he cries in order to avoid upsetting other occupants of the house.

Table 3 indicates that only 45·4% of the family-units had a home to themselves. The average number of family-units per house was 1·68 in social classes I-II, 1·66 in social class III, and 1·98 in social class IV-V. The majority of family-units who were sharing houses were living with the baby's grandparents while trying to find a home of their own. The disadvantage of the dual regime for the baby has to be offset against the probability of help with the housework for the mother. On the record forms a note has been made whether or not the mother has had any help with the housework, but the results have not been analysed in bulk as it has been difficult to draw the line between the different types of help this term might cover. For instance, at one end of the scale it may refer to a household which has a nanny and domestic help, and at the other end of the scale to the husband helping to dry the supper dishes. Incidentally, the mothers' comments on the help their husbands give have varied greatly. Some cook the Sunday joint; some do nothing. The wife of a chef, when asked if he did any cooking at home, said that she would not let him do so as he left such a trail of washing-up behind him. 'Mass Observation Bulletin' (June, 1948) stated that of its panel, nine out of ten male members of middle-class households expected to help with domestic work, and nine out of ten women thought it right that they should do so. Where, after her confinement, the mother has been able to have a home help this has been much appreciated.

Number of Persons in the House. Note was made of the number of children and the number of adults

TABLE 3

ONE FAMILY-UNIT PER HOUSE OR SELF-CONTAINED FLAT

	Social Class			In All Social Classes
	I-II	III	IV-V	
No. of houses in sample	76	319	76	471
No. of family-units living alone in house or flat	33	150	31	241
No. of family-units living with friend(s) or relation(s) as part of their own household	21	94	22	137
No. of multiple households in same house	22	75	23	120
Percentage of family-units living alone in house or self-contained flat	43·4	47·0	40·8	45·4

in both the household and the house. The number of persons in the house is shown in Table 4. These figures give some indication of the number of persons who had to share the same lavatory and other amenities.

Table 4 shows that the average number of persons per house in all social classes is 5·6. In the Manchester Billeting Survey (1945) the average number of persons per occupied house was 3·25. Data from the last census (1931) gives the average for Oxford County Borough Council as 4·10 then; for Manchester Borough Council as 4·10; for England and Wales as a whole as 4·17. On the other hand, the rooms per occupied dwellings are given as 5·67, 4·72, and 5·07 respectively for that date, whereas, considering the Child Health Survey homes only, the average number of rooms per house was 6·42 in social classes I-II, 5·22 in social class III, and 5·13 in social classes IV-V.

Density (Number of Persons per Room). As might be expected, the density at which families were living was highest in the lower social classes, the average number of persons per room being 0·83 in social classes I-II, 1·06 in social class III, and 1·31 in social classes IV-V. Data from the 1931 census give the average number of persons per room as 0·72 in the Oxford County Borough, as 0·87 in the Manchester County Borough, and as 0·83 in England and Wales as a whole, whereas the average in the Child Health Survey for all social classes has risen to 1·06 persons per room.

Table 5 shows the proportion of families living at different densities and the difference between the social classes is evident. When the household only is considered a higher percentage of families is living at a density of more than one person per room than when the whole house is considered, reflecting the fact that 11 families were each living in one

TABLE 4

DISTRIBUTION BY NUMBER OF PERSONS IN THE HOUSE

No. of Persons (Adults and Children)	Social Class			All Social Classes
	I-II	III	IV-V	
2–5	50	212	30	292
6–10	24	101	41	166
11–15*	1	5	3	9
16* and over	1	1	2	4
Total no. of survey families	76	319	76	471
Average no. of persons per house	5·3	5·3	6·7	5·6

* The two families where there were 37 persons in one house were 'squatters' who took over an empty hotel. The family living where there were 12 persons to a building were squatters in the hotel annexe.
The family living where there were 22 persons in the house, was that of a housemaster at a boys' preparatory school.
The family living where there were 19 persons was one of four adults and an illegitimate child, living in three rooms in an old tenement house shared by four families consisting of twelve adults and seven children living in the nine rooms.
The family living where there were 14 persons in a house was one of four people (children aged 4½ and 1 year) living in a bed-sittingroom at the top of an old tenement house where six families (14 persons) lived in seven rooms.

TABLE 5

DISTRIBUTION BY NUMBER OF PERSONS PER ROOM PER CENT.

Density	Whole House				Household Only
	Social Class			All Social Classes	All Social Classes
	I-II	III	IV-V		
Under 1 person per room	60·5	38·6	17·1	38·6	33·8
1+	38·2	59·6	69·7	57·7	58·9
2+	1·3	1·9	13·2	3·6	7·2
	100·0	100·1	100·0	99·9	99·9

bed-sitting-room, in houses not otherwise exceptionally overcrowded. Seven families were living at three to the one room, two families at four to the one room, and two families at five to the one room.

Type of Housing. In appraising housing the standards used were, of necessity, personal standards, but individual differences of opinion were eliminated as far as possible, as one social worker only was engaged in the survey at one time.* Assessments were re-checked at the subsequent visits and, in cases of doubt, as with the older and more dilapidated houses, the opinion of the Sanitary Inspector was sought as a further countercheck.

Approximately half the houses in the survey were comparatively new. Of the total number, 205 were built before 1900; 33 were built between 1900 and 1920; 230 were built after 1920. Two were unclassified. It was noted whether or not the house was condemned, but at present this has no strong significance as some houses in reasonably good condition were technically condemned before the war for purposes of town planning. Others, now in less good condition, are not yet condemned, for it is useless to condemn a house if there is no immediate prospect of re-housing the occupants. A special entry was made when a house was low-lying, in an area subject to flooding, or on the hills on the outskirts of the town, but as the variation is only between 200 and 350 feet above sea-level these notes have not been analysed.

STATE OF REPAIR. This has been assessed as 'fair' when only minor repairs would have been required to put the house in order, and 'poor' where more extensive work was necessary. Frequently those houses classified as being in poor repair were condemned before the war, and extensive repairs are not therefore contemplated.

VENTILATION. In assessing ventilation note was taken of the size of the rooms, the size and position of windows for cross ventilation, and whether the house had through ventilation or whether it was built back to back. Where the potential ventilation has been good, but windows seldom opened, the ventilation from the point of view of housing details has been classed as good, but 'fresh air in relation to the baby' has been down-graded. The only back-to-back houses in this series were some old cottages in Wolvercote. The general picture for Oxford is clearly much more favourable than that obtaining, for instance, in a northern industrial town or in many parts of London.

LIGHT. In the assessment of lighting, this was classed as 'fair' where the side of the room appeared dim, and as 'poor' where the lights had to be on during the day or where, but for economy, it would have been an advantage to have artificial lighting during the day. The majority of the houses were lit by electricity.†

DAMP. The mother was particularly asked whether the house was damp at the first visit and after the first winter, and if she maintained that there was no damp, her statement was accepted. If, however, she said the house was damp, this was investigated and recorded as 'ground damp,' 'damp walls,' or actual 'leaks,' and, where necessary, this was confirmed with the Sanitary Inspector. No attempt at measuring the actual extent of the damp has yet been made. Of the 471 houses, 40 were recorded as having ground damp, 100 were recorded as having damp walls, and 18 as having actual leaks. Flooding in the spring of 1947 also led to the temporary recording of damp, as many of the houses in the central area had flooded basements.

The analysis of the housing conditions has been

* For the period 1944-46 the social reporting was in the hands of Miss Elisabeth J. Williams. After a month of joint work the reporting has been the responsibility of the writer.

† The three visits were at different times of the year.

TABLE 6

DISTRIBUTION IN RESPECT OF REPAIR, VENTILATION, LIGHT AND DAMP: ALL SOCIAL CLASSES

	Good	Fair	Poor
Repair	74·5%	20·6%	4·9%
Ventilation ..	76·2%	21·7%	2·1%
Light	74·5%	22·3%	3·2%
Damp	72·8% (i.e. no damp)	27·2% (i.e. any form of damp)	

summarized in Table 6. As would be expected, the quality of the houses in respect of repair, ventilation, light, and damp was poorer in the lower social classes.

COUNCIL HOUSES. At the time of the original enquiry, 53 of the families were living in Council houses and 409 in houses built by private enterprise (nine unclassified). Any later analysis will show a higher proportion of Council houses, reflecting re-housing in the prefabricated houses on the new estates, in addition to re-housing in the older Council houses. Only one family from social class I-II lived in a Council house.

FLATS AND TENEMENTS. Thirty-two homes were self-contained flats, either built as such or converted, and four homes were in tenement buildings.

Household Conveniences. These are analysed as percentages of the sample in Table 7.

BATHROOMS. As will be seen from Table 7, 70% of the families had access to a bathroom (the proportion again varying with the social class). In addition, many families managed with a zinc bath in the scullery, with water heated in the copper, for all the houses in this series had water from the main or a tap in the house. Where a small old house had a built-in bath added, this again was often in the scullery which, in many cases, was a later addition to the house, built on at the back.

Baths were, however, out of the question for any family living in rooms at the top of an old house where the only water tap was down in the basement. One mother carrying water under these circumstances fell downstairs and had a miscarriage. She has since been re-housed in a 'prefab' and the all-round standard of cleanliness has risen considerably. The increase in the cleanliness of the children is not so great as the increase in the cleanliness of the house. This is as would be expected, for when water was a more prized commodity, the children came first and an effort was made to keep them reasonably clean, though not nearly as much effort was put into cleansing the two shabby and overcrowded rooms. Since re-housing over a year ago, the new home has been kept at a good standard of cleanliness, and the children are delighting in playing in a garden for the first time.

It is not possible to make comparisons between the homes of the children in the survey and those in other selected areas of the country, but the Medical Officer of Health for Manchester has

TABLE 7

HOUSEHOLD CONVENIENCES

Bathroom	Bathroom per family	62·5%
	Bathroom shared	7·7%
	No bathroom	29·8%
Laundry facilities	Constant hot water, Airing cupboard, Outdoor drying	43·9%
	Less one of the above	51·6%
	Less two or three of the above	4·5%
Cooking facilities	Gas cooker	59·7%
	Electric cooker	37·1%
	Other methods	3·1%
Sanitation	Indoor	61·8%
	Outdoor only	38·2%
Larder	Larder or refrigerator	65·2%
	No larder or refrigerator	34·8%
Garden	Garden	91·1%
	No garden	8·9%

kindly supplied an extract from a Billeting Survey (1945) giving the percentage of occupied houses having baths. This varied from 15·03% in the central area to 84·94% in the southern area, with an average of 59·14% for the total Manchester area,* whereas the percentage of the Child Health Survey homes with baths was 70·28.

LAUNDRY FACILITIES. 'Good' laundry facilities were taken to mean that the following were available: (1) Constant hot water, either heated by a fire boiler, a copper or an immersion heater; (2) an airing cupboard; (3) drying space, i.e. yard or garden.

'Fair' laundry facilities indicate that one of these facilities was lacking; often the airing cupboard, for, although 204 families had good laundry facilities, 270 had constant hot water. As can be imagined, where there is no airing cupboard and there is a baby in the house, napkins are constantly draped around for airing and usually the only fire is in the living room—which may also be the kitchen. 'Poor' laundry facilities were taken to mean that at least two of the three facilities were lacking.

SOAP. When the survey was first started a double soap ration was allowed only for infants up to the age of one year. At the end of 1947 this concession was extended until the infant's second birthday, and this, though belated, was much appreciated by the mothers who had all been maintaining that there was far more washing to do in the second year than in the first year. This is readily understandable, for the infant's peak period for starting to crawl (interpreted as any form of locomotion) is between 9 and 10 months. In a series of 334 children, 37·7% were said by their mothers to have taken their first steps by the age of 12 months, and though 94·9% had taken their first steps by the age of 18 months this by no means implied that the child had habitually assumed an upright posture at this stage. Also, the child cannot be relied upon to be clean and dry during the day and can be trusted still less to be dry at night, as Table 8 shows. For interest the infants were divided by sex, and the superiority of the girls over the boys in this respect is shown to be statistically significant (Table 8). These figures must be interpreted as being on the optimistic side, as they are based on information given by the mothers at the six-monthly clinical examinations, and ignore the occasional lapses afterwards.

TABLE 8

	Boys		Girls		Both Sexes	
	No.	%	No.	%	No.	%
Clean and dry—day						
At 1 year ..	24	13·8	30	18·8	54	16·2
At 18 months	82	47·1	100	62·5	182	54·5
Clean and dry—night						
At 1 year ..	3	1·7	8	5·0	11	3·3
At 18 months	26	14·9	33	20·6	59	17·7
Total sample ..	174	100·0	160	100·0	334	100·0

SANITATION. The majority of homes had indoor sanitation. Eleven homes had indoor and outdoor sanitation. In this series all had water closets, for all the babies started life in the town. Some later moved out into the country and still remained in the survey, so that subsequent analyses will show a small proportion of earth or chemical closets. No note has been made of how many people shared one lavatory, but, indirectly, some impression can be gained from the tables, given earlier, which indicate the number of families and individuals in one house.

LARDERS. In spite of the relatively high proportion of larders, the impression gained is that the majority of mothers were in the habit of shopping daily. No specific records have been made on this subject, but those who have commented have mentioned that they shopped daily for vegetables in particular. The prefabricated bungalows are supplied with built-in refrigerators, but otherwise refrigerators were exceptional.

GARDENS AND ALLOTMENTS. As is shown in Table 7, 91% or 429 families had gardens and of these, at the time, 190 grew some vegetables. In addition, 42 families had allotments when first asked. Of the families without a garden, a proportion had backyards, which is a factor when considering how much time the child spends out of doors. Many of the old houses, however, which are built in rows, have back doors which are so narrow that a pram cannot be taken into the backyard or garden, and, as the front door opens straight on to the street, the pram has to be put on the pavement.

Cost of Food

The mother was not asked to work out how much she was spending on food for her family until the

* Manchester water is very soft, total hardness (as $CaCO_3$) being about 3·6 parts per 100,000. On the other hand, atmospheric pollution is high, the mean monthly deposit varying from 10·01 to 35·36 tons per month per square mile according to the district of Manchester (M.O.H. Report, 1946). The Oxford water supply is hard, total hardness being given as 22 parts per 100,000, but the atmosphere shows such a small degree of pollution that no regular readings are taken (M.O.H. Report, 1946).

baby was at least a year old, and this request was always framed in such a manner that she could have refused quite easily. In fact, there were only two point-blank refusals: once when the mother said the cost of food would be ' too high ' and once where the family was obviously living a hand-to-mouth existence and the simple arithmetic involved was said to be too difficult.

Even so, figures have not yet been obtained for all families. There are a number of reasons for this. The largest group consists of those mothers who ' forgot ' (which is understandable where there is a gap of six months between the visits), and who will later have the figures for us. Another group includes families in which the paternal grandmother was doing the housekeeping for all, and the mother felt it would not be politic for her to make these enquiries. A third small group has been omitted because a substantial proportion of food has not been paid for at market prices; for instance, where the father owns a small shop, or where supplementary food is brought home as a perquisite, particularly from the colleges.

It was noted if vegetables were grown, either on an allotment or in the garden, and whether hens were kept. One or two mothers kept goats, one having been advised to try feeding her baby, who had infantile eczema, on goat's milk. One had a cow.

The Institute of Statistics (Oxford) has studied the pattern of food expenditure of families who were asked to keep details of expenditure on food during particular fortnights, for example, in the summer of 1947, but it was not possible, with our larger numbers, to ask for more than an approximate figure. Whenever practicable, the mother was asked to keep a record for a four-week rationing period and to divide the total by four, but it was not always possible to insist upon this. Sometimes the answer was arrived at by reckoning up how much had been spent at each type of shop. This was often very revealing and gave useful guidance when the quality of an older child's diet was assessed. For instance, the number of loaves bought during the week is fairly indicative of the types of breakfast and high tea, especially if it is also known that the father does not take sandwiches for mid-day, but has a meal at a canteen.

The figure spent on food for the household has been divided by the number of adult-units, each child under ten being counted as half an adult-unit (an approximation of the Cathcart and Murray family coefficient scale).

Table 9 shows remarkably little difference between the social classes, as would be expected in an age of rationing, the average cost of food per adult-unit per week being 16·12 shillings in social classes I-II, 15·63 shillings in social class III, 15·18 shillings in social classes IV-V, and 15·62 shillings in all social classes.

The figures obtained do not relate to any specific week or season during the period 1945-47. At present each family has only been asked for this information once, but several mothers who were first asked in 1945-46 have recently commented that the figure has risen considerably. It is, however, difficult to disentangle how much of this rise is due to the rise in the cost of food itself and how much has been due to the increase in the amount of unrationed foods (especially fruit) for sale in the shops, coupled with the greater amount of money available for food, particularly after demobilization. The amount of money spent on food for the family is now the only item of the budget asked for from

TABLE 9

DISTRIBUTION BY NUMBER OF SHILLINGS SPENT ON FOOD PER ADULT-UNIT WEEK

Shillings	Social Class			All Social Classes
	I-II	III	IV-V	
Less than 9	—	10	2	12
10–14	17	91	29	137
15–19	17	76	9	102
20–24	7	37	7	51
25–29	2	5	3	10
30 plus	—	1	1	2
Total number of families ..	43	220	51	314
Average cost per adult-unit (in shillings)	16·12	15·63	15·18	15·62

all families. When the survey was first started other items were obtained, but in practice it was found that the figures could not stand comparison statistically. For instance, many of the mothers did not know their husbands' incomes and could only say what they were given for housekeeping, which covered different items of expenditure in different families and so could not be used for comparative purposes. Similarly, although rent was at first asked for, this might mean anything from rent paid for an unfurnished house or payments to a building society, to 'rent' for two furnished rooms which would cover rates and possibly lighting and heating, or else payment to relatives for board and lodging. These figures are of interest when considering individual families, but are of little use when required for statistical comparison, and so are no longer asked for. They are, however, noted when the information is volunteered. For instance, many mothers have commented on the increased rent when the family has been re-housed in a 'prefab' after living in an old house in the centre of the city where the rent was low.

Summary and Conclusions

It is now generally recognized that deaths in infancy constitute a twofold problem. One phase is represented by stillbirths and neonatal mortality in which obstetrical and nutritional factors are probably of major importance; the other by deaths of babies in the later stages of infancy which are more directly influenced by environment. It seems probable that health and sickness experience and growth and development may also be related to environmental opportunity, and the further purpose of the Oxford survey is to discover what correlations can, in fact, be established. The picture here presented is that of the material conditions surrounding infancy in the main social groups of a city salubrious by comparison with many London boroughs and industrial cities of the North, Midlands, and South Wales. The County Borough of Oxford has for some time returned one of the lowest infant mortality rates in the country. In 1947 the value was 29, compared with the national figure of 41 per 1,000 live births. In this connexion it is well to remember that Oxford was one of the earliest cities with voluntarily provided maternity and child welfare services before these became the responsibility of the municipality.

In this study the social background of 471 babies, born to mothers of different social groups during the period, has been considered under the following main headings: (*a*) Material environment (housing, amenities); (*b*) social and economic environment (parents, occupations, budget); (*c*) associated human environment (family, household, density); (*d*) maternal environment (health, efficiency, breast-feeding). The conclusions are as follows.

Material Environment. The majority of the houses were considered to be structurally satisfactory; more than 70% were free from damp, and for 75% the ventilation and light were scaled as 'good.' As would be expected, the household amenities varied for the different social groups and this variation reflected the difficulties which the mothers experienced in coping with the baby's requirements. In the overall picture, 30% of the houses had no bathroom; nearly 40% had neither a larder nor a refrigerator; good laundry facilities were available only to 44%, and 38% had outdoor sanitation only.

Associated Human Environment. The density at which the families were living showed an increase in the lower social groups and also confirmed that there was now generally more overcrowding than that disclosed by the 1931 census. Only 45% of the family units were living on their own. Accordingly, the care and upbringing of the baby was rendered difficult by the interference of too many 'mothers' in the household. Of the 471 families, 220 infants were only children at the time of enquiry, though not necessarily the firstborn, as, in this instance, stillbirths and siblings who had not survived were not considered. There were two children in each of 143 families, from four to nine children in 45 families and more than 10 surviving children in three families. This pattern of distribution accords closely with that for England and Wales in 1946.

Social and Economic Environment. There was a preponderance of children representing social class III in the survey, a result to be expected since this group is numerically the largest in the country generally. Unemployment among the fathers was negligible and 33 mothers were working before the infant was a year old, eight being separated from their children while working. The amount of money spent on food per adult-unit per week varied considerably within the social classes, but between the social classes the average only varied by a shilling. The average for all social classes was 15·62 shillings.

It remains to be seen whether the clinical, somatometric and radiographic studies will reveal any significant differences in respect of the health, sickness, and growth of children in the pre-school years under the diverse environmental opportunities here discussed.

Thanks are due to the medical officers, health visitors, and the chief sanitary inspector of the Public Health Department of the City of Oxford, and to my colleagues in the Child Health Survey. I am indebted to the late Professor J. A. Ryle and Dr. W. T. Russell for their help and advice in the preparation of this paper.

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BRITISH PAEDIATRIC ASSOCIATION

PROCEEDINGS OF THE TWENTY-FIRST GENERAL MEETING

The twenty-first annual meeting of the British Paediatric Association was held at Windermere on April 26, 27, and 28, 1950.

Business Proceedings. The President, Dr. A. G. Maitland-Jones, was in the chair and the following members were present:

Drs. F. M. B. Allen, E. C. Allibone, I. Anderson, H. T. Ashby, C. Asher, H. S. Baar, J. M. Bligh, R. E. Bonham Carter, F. Braid, J. V. Braithwaite, R. W. Brookfield, H. C. Cameron, W. H. P. Cant, N. B. Capon, I. A. B. Cathie, C. Chisholm, W. R. F. Collis, T. Colver, B. D. Corner, D. Court, W. S. Craig, M. Creak, J. Crooks, V. M. Crosse, G. Davison, R. H. Dobbs, E. Dott, A. C. Doyne Bell, R. W. B. Ellis, P. R. Evans, G. B. Fleming, F. J. Ford, A. W. Franklin, D. Gairdner, W. F. Gaisford, S. Graham, C. K. J. Hamilton, C. F. Harris, E. W. Hart, J. D. Hay, J. L. Henderson, D. V. Hubble, J. H. Hutchison, R. S. Illingworth, R. C. Jewesbury, H. E. Jones, F. F. Kane, R. Lightwood, P. MacArthur, A. MacGregor, H. M. M. Mackay, R. Marshall, C. McNeil, F. J. W. Miller, A. Moncrieff, A. E. Naish, A. V. Neale, G. H. Newns, D. N. Nicholson, J. N. O'Reilly, L. Parsons, C. G. Parsons, W. W. Payne, C. P. Pinckney. B. E. Schlesinger, W. P. H. Sheldon, W. C. Smallwood, R. E. Smith, J. C. Spence, R. E. Steen, K. H. Tallerman, M. L. Thomson, C. W. Vining, H. K. Waller, A. Wallgren, J. F. Ward, A. G. Watkins, K. D. Wilkinson, M. J. Wilmers, D. W. Winnicott, W. G. Wyllie.

The Association had the honour of entertaining 35 guests.

The MINUTES of the last Annual General Meeting were approved.

Rule 2 was altered to read as follows:

> "It shall consist of Ordinary Members, Honorary Members, and Corresponding Members. Ordinary Members shall be actively engaged in the practice or teaching of paediatrics or in paediatric research and shall have contributed to the advancement of paediatrics."

ELECTION OF OFFICERS. The following were elected by ballot for the year 1950-51.

PRESIDENT. Prof. J. C. Spence.

TREASURER. Dr. R. C. Lightwood.

SECRETARY. Prof. Alan Moncrieff.

EXECUTIVE COMMITTEE

REPRESENTATIVES FOR LONDON. Dr. R. E. Bonham Carter; Dr. C. T. Potter and Dr. B. E. Schlesinger (new members).

REPRESENTATIVES FOR THE PROVINCES. Dr. G. Davison (Newcastle-on-Tyne); Dr. D. V. Hubble (Derby); Prof. R. S. Illingworth (Sheffield).

REPRESENTATIVE FOR SCOTLAND. Dr. James Hutchison (Glasgow).

REPRESENTATIVE FOR IRELAND. Prof. F. M. B. Allen (Belfast).

ELECTION OF NEW MEMBERS. The following were elected by ballot to membership of the Association:

(a) HONORARY MEMBERS
- Sir John Charles
- Dr. A. G. Maitland-Jones
- Dr. R. Marshall
- Prof. C. B. Perry.

(b) CORRESPONDING MEMBERS
- Prof. A. Eckstein (Hamburg)
- Prof. P. Plum (Copenhagen)

(c) ORDINARY MEMBERS
- Dr. T. E. D. Beavan (Chester)
- Dr. M. Bodian (London)
- Dr. J. L. Emery (Sheffield)
- Dr. R. C. MacKeith (London)
- Dr. R. A. Miller (Edinburgh)
- Dr. A. P. Norman (London)
- Dr. Victoria Smallpeice (Oxford)
- Dr. H. Parry Williams (Coventry)
- Dr. Winifred Young (London).

The TREASURER'S REPORT was received and approved.

The REPORT OF THE EXECUTIVE COMMITTEE was received and approved and is printed below.

NEXT MEETING. It was agreed that the Executive Committee should consider the question of inviting a group of paediatricians from abroad to the meeting in 1951.

Report of the Executive Committee 1949-1950

Since the last Annual General Meeting held at Windermere in May, 1949, the Executive Committee has met on three occasions. The following is a summary of the main activities during the year.

1. APPOINTMENTS AND DISTINCTIONS. Congratulations were sent to Dr. Lorimer Dods, a corresponding member, on his appointment to the Chair of Child Health in Sydney and to Dr. A. G. Watkins on his appointment to the Chair of Child Health in Cardiff.

2. MEMBERSHIP. Aided by two reports from a sub-committee, the Executive Committee has given very careful consideration to the whole problem of membership. As a result, a change in Rule 2 is being moved at the Annual Meeting, and contributions to the advancement of paediatrics will henceforth be essential before candidates can be nominated.

3. SWEDISH GUESTS. The most memorable event of the year was the visit of 30 Swedish paediatricians, some of them with their wives. The London programme included visits to the Hospital for Sick Children, Great Ormond Street, and to the Queen Elizabeth Hospital for Children at Banstead, together with an evening reception by the British Medical Association and a dinner by the British Paediatric Association at the Apothecaries' Hall. The Windermere Meeting was much enjoyed by guests and hosts alike. A special supplement to *Acta Pediatrica* was subsequently dedicated to the British Paediatric Association, a friendly gesture of gratitude which was keenly appreciated.

4. WINTER MEETING. A two-day gathering in London in November brought together 230 members of the British Paediatric Association and of the Society of Medical Officers of Health—Maternity and Child Welfare, School Health Service and Fever Hospital Groups. During the meeting Prof. St. G. Huggett delivered the George Frederic Still Memorial Lecture for 1949. An evening reception was held at the Royal Society of Medicine.

5. INTERNATIONAL PAEDIATRIC CONGRESS, 1950. Arrangements have been made during the year to secure adequate representation of British paediatrics. The Treasury has agreed to allow 20 ' delegates ' to secure special currency and it is hoped that others will be able to go on basic travel allowances. A list of centres in Great Britain willing to receive visitors between August 7 and 12, 1950, has been forwarded to the organizers of the post-congress tours.

6. PAEDIATRIC ADVICE IN THE NATIONAL HEALTH SERVICE. Steps were taken during the year to deal with complaints that in some hospital regions there was no machinery for seeing that the Boards received advice on paediatric matters. The Executive Committee has also under discussion the question of a central paediatric advisory committee.

7. NURSING OF SICK CHILDREN. The Nurses Act, 1949, leaves untouched at present the special register for sick children's nurses, but the situation, it is felt, requires careful watching. Representations have been made at the appropriate levels to attempt to secure paediatric members for all area nurse-training committees.

8. ARCHIVES OF DISEASE IN CHILDHOOD. Dr. Eric Sims of Adelaide has been appointed to succeed Dr. Helen Mayo on the general advisory board.

9. STANDING COMMITTEES AND SPECIAL SUB-COMMITTEES. During the year the report of the cross infection committee was published by Prof. A. G. Watkins in association with Prof. E. Lewis Faning. A joint committee with the Royal College of Obstetricians and Gynaecologists has been set up to study problems of prematurity, and replies to a request from Dr. Percy Stocks of the Registrar General's Office on definitions of live birth and foetal death were also prepared in association with this College. A sub-committee prepared evidence for the Ministry of Health special committee on speech therapists, and the child psychology sub-committee dealt with the problem of the training of lay psychotherapists. A sub-committee on the training of paediatric specialists is still considering the subject. Three members of the Association were appointed to assist the Distinction Awards Committee. Numerous requests for information and advice have been received during the year and undoubtedly the Association is becoming recognized as the authoritative body on many topics. Special mention may be made of questions on the spacing of bars on cots, the dangers of infection in dried milk, and the specifications for children's catheters.

10. JOINT MEETING WITH VISITING PAEDIATRICIANS. Canadian colleagues were finally unable to accept an invitation to a joint meeting in this country before the Zurich congress. It is hoped, nevertheless, that such a joint meeting may one day be arranged.

11. The Executive Committee were pleased to welcome Dr. C. Asher as an observer appointed by the Ministry of Education.

12. The Executive Committee heard with sorrow of the death of Dr. J. S. Y. Rogers of Dundee, one of the original members of the Association and a loyal supporter of its activities for many years.

Communications

DR. C. BALF (Edinburgh). 'Late Prognosis of Intracranial Injury at Birth.' In a follow-up investigation of mature babies born in 1945-47 at Simpson Maternity Pavilion, Edinburgh, three groups were distinguished: (1) Controls (pregnancy, labour, and neonatal period normal); (2) asphyxia neonatorum of which A.I (slight) comprised 7·4% and A.II (severe) 2·6% of all mature births; (3) babies with signs of cerebral irritation. Three sub-divisions were made, namely, C.I with minimal signs lasting less than two days, C.II with definite signs resolving within four days, C.III with severe persistent signs.

Mothers were asked to bring their children for interview and examination lasting approximately one hour; 18% could not be traced, and of the remainder 73% attended.

TABLE

	Total	Attended	R(%)	X(%)	T(%)	N(%)	Fits Only (%)
Controls	45	30	3·3	6·7	0·0	0·0	3·3
A.I	108	61	8·2	11·5	1·6	0·0	1·6
A.II	39	23	*26·0	*26·0	4·3	0·0	0·0
C.I	45	27	*11·0	11·0	0·0	0·0	0·0
C.II	60	36	*11·0	5·6	*8·5	2·8	2·8
C.III	48	31	*26·0	6·5	*12·9	*16·0	6·5

R = Undue restlessness in infancy without detectable cause.
X = Maladjustment excluding all normal reactions to environment.
T = Post-asphyxial syndrome. N = Neurological defects.

Percentages marked * are significant though they still depend on indefinite clinical assessment.

Neurological sequelae, which were found in six cases, included hemiplegia, monoplegia, and mental defect.

Asymmetrical palsy was associated with persistent neonatal signs. Behaviour disorders rarely constituted a clinical problem at this age, but further enquiry in the later age groups is needed.

MR. J. M. ROBERTSON (London). 'Young Children in Hospital.' Recent advances in knowledge of child development have established that the ability of the individual to achieve mental health is largely dependent on the experience of a stable, affectionate relationship to a mother or mother-substitute in the first four or five years of life, and that severe breaks in the continuity of such relationships may lead to serious personality disorders.

Dr. John Bowlby, who has been reviewing all the evidence on the matter on behalf of W.H.O., reports remarkable and convincing agreement on the adverse effects of maternal deprivation in a large number of clinical and statistical studies—often by people working independently of each other. Psychiatric clinics give many instances of child and adult patients whose personality disorders originated in loss of mothering, including that caused by long periods in hospital.

Though young children may seem to adjust to hospital after a few days of fretting, there is evidence that after even a short stay in hospital very many of them show marked emotional disturbances for weeks or months on returning home. Research has still to show whether these disturbances clear up completely, or whether scars remain which may be reactivated as personality disorders in later life.

There is no longer any doubt that separation of the young child from his mother is a disturbing experience which may lead to permanent damage to his mental health, and that length of separation and quality of separation environment (in terms of opportunity for making stable affectionate relationships) are of great importance. It is therefore urgent that paediatricians should discover the limits within which techniques of nursing care can safeguard the mental health of young children in hospital.

DR. DAVID LAWSON (London). 'An Inclusive Classification of the Intracranial Tumours of Childhood. Based on a Study of 130 Cases.' A study of 130 cases of intracranial tumour in childhood, occurring over a 21-year period, resulted in the classification of these tumours in terms of the following disease entities which were described and defined:

Glial Tumours		116
Differentiated medulloblastoma	50	
Supratentorial	14	
Subtentorial	36	
Fully differentiated cerebellar astrocytoma (22 were fully circumscribed)	33	
Subependymal astrocytoma	8	
Diffuse fully differentiated astrocytoma of field origin (pons, cerebral peduncles, mid-brain, basal ganglia, hypothalamus and optic nerves)	21	
Unclassified supratentorial glial tumours	4	
Non-Glial Tumours		14
Adamantinoma	6	
Meningeal tumour	4	
Choroid plexus tumour	3	
Pinealoma	1	

Management and prognosis were briefly discussed, and the age incidence and site of origin of each group were illustrated by charts.

The term 'differentiating medulloblastoma' covers a broad range of differentiating tumours arising from a primitive cell, from the undifferentiated

'medulloblastoma' of the cerebellum to the fully differentiated 'oligodendroglioma' of the cerebral hemispheres.

The impossibility of accurate pre-operative diagnosis of tumour type makes full investigation and treatment a matter of urgency in almost every case, although total excision and recovery will rarely be possible except with the circumscribed cerebellar astrocytoma. Given early diagnosis and first-class neurosurgical technique, the mortality here should be negligible and the children should survive unscathed.

In the 21-year series of circumscribed cerebellar astrocytomata, 15 out of 22 children are well and symptom-free after total excision. For the last decade, the comparative figures are 12 out of 14.

DR. GEORGE DAVISON (Newcastle-upon-Tyne). 'Acute Nephritis Presenting as Heart Failure.' A case of acute nephritis was reported in which heart failure dominated the picture so that the true nature of the illness was obscured.

Goodhart (1879) wrote of 'Acute Dilatation of the Heart as a Cause of Death in Scarlatinal Dropsy.' In 1938 Rubin and Rapoport reviewed a series of 55 cases of acute nephritis, and found evidence of cardiac involvement in 14. In a series of 64 cases of acute nephritis treated at the Newcastle General Hospital the only death was due to congestive heart failure, and in eight other patients there was evidence of heart failure. In three the predominant symptoms on admission were those of severe heart failure.

The illness described would be compatible with a diagnosis of acute nephritis but for the absence of urinary changes. In 1948 Crofton and Truelove described a case in a girl of 16 in whom they made a diagnosis of acute nephritis in the absence of urinary abnormality, and referred to cases described by Fenini in 1872, and by Henoch in 1899. Alessandri and Roeschmann described in 1942 a man aged 32, admitted with hypertension and congestive failure, who died on the third day and in whom the histological diagnosis was acute glomerular nephritis.

Acute glomerular nephritis is an illness characterized by widespread tissue changes, in which different organs may be involved in varying degrees. The diagnosis of acute nephritis should be considered in the event of sudden heart failure in a child, even when there is no abnormality in the urine.

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DR. S. F. SCHOFIELD (Manchester). 'The Effect of Toxaemia of Pregnancy upon the Neonatal Kidney.' In the first part of the investigation, which was carried out with D. C. A. Bevis, the kidney weight of 38 normal infants and 19 infants whose mothers had toxaemia was compared with the body weight. A constant differential growth ratio was found to exist between the two. It was the same in both groups and for neonatal deaths and stillbirths alike.

Histologically, the degree of glomerular development was found to be the same in both groups and no lesions were seen similar to those found in mothers dying of eclampsia.

Urea clearances were estimated on nine toxaemic and eight normal infants. No statistical difference between the two groups was found but the blood urea concentrations of the toxaemic infants were consistently higher than those of the normals.

By using oscillometry and a 2·5 cm. cuff, 10 toxaemic infants were found to be hypertensive compared with 10 normals.

Lastly, the incidence of albuminuria in 52 normal infants and 17 toxaemic infants was found to lie within the same limits.

It was suggested that these findings may be explained on the basis of the renal shunt described by Trueta.

DR. HUGH R. JOLLY (London). 'A Study of Sexual Precocity.' A study of 44 cases of sexual precocity from London hospitals, all seen personally except for three from post-mortem records, gave the following results.

CASE ANALYSIS

Cerebral	Constitutional	♀	22
		♂	3
	Organic	Inflammatory	1
		Neoplastic	4
		Degenerative	1
Adrenal	♂	Carcinoma	2
		Hyperplasia	3
	♀	Carcinoma	1
Gonadal	Granulosa cell tumour of ovary		1
	Interstitial cell tumour of testis		2
Miscellaneous	Albright's syndrome		1
	Hepatoblastoma		1
	Female pseudohermaphrodites		2

Cerebral: True puberty (spermatogenesis or ovulation) occurred only in this group. Frequency

of constitutional precocity in girls emphasized its importance. Organic cerebral diseases only cause precocity if the lesion involves the posterior hypothalamus and the pituitary is intact.

Adrenal: Is due to cortical overactivity. In boys, it should be differentiated from the constitutional group by small testicles (no spermatogenesis) and much higher 17-ketosteroid figure. In girls, feminizing tumours are exceptionally rare.

Gonadal: Granulosa cell tumour is extremely rare as a cause of precocity, and girls should only be subjected to laparotomy if the mass is palpable.

Miscellaneous: One boy with Albright's syndrome showed precocity. One boy had only hepatoblastoma. Two cases of female pseudohermaphroditism due to adrenal hyperplasia were included, since these usually presented as cases of precocity.

DR. C. G. PARSONS (Birmingham). 'Auricular Septal Defect.' A boy of five years had repeated attacks of severe bronchitis and pneumonia, and on several occasions he was expected to die. He had an auricular septal defect with greatly enlarged right auricle and ventricle, aneurysmal dilatation of the pulmonary artery, pronounced vascular engorgement in the lungs, and signs of congestive heart failure. Mr. A. L. d'Abreu closed the septal defect by Murray's (1948) method. A continuous electrocardiogram taken during operation showed practically no disturbance of cardiac rhythm. After operation the reduced intensity of the pulmonary second sound and the diminished pulsation in the arteries at the hilum indicated a fall in pulmonary blood pressure, but the heart was still enormous. An attack of bronchitis after operation caused no anxiety; exercise tolerance had increased.

Two unsuccessful cases, illustrating diagnostic and operative difficulties, were described.

Operative risks are such that surgery should at present be reserved for children whose life is seriously threatened by recurrent pneumonia or heart failure. Ventricular septal defects may exactly mimic auricular septal defects, and the two conditions can be differentiated only by catheterization, although even this method of diagnosis is not infallible.

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PROF. A. WALLGREN. 'The Declining Birth Rate: A Medical and Social Problem.' To be published in full.

DR. H. BICKEL (Birmingham). 'Observations on Amino-aciduria in Children.' The investigations were carried out by means of paper chromatography, which provides a specific test of each amino-acid in blood, urine, and other biological fluids. The normal urine chromatogram was based on a study of 100 school children and 50 infants. The amino-acidurias in 700 chromatograms of blood and urine from children with liver, kidney, and other metabolic disorders may be classified as (1) overflow mechanism with high blood level (liver diseases, newborns); (2) renal mechanism with normal or low blood level (proximal tubular dysfunction in kidney diseases); (3) unexplained mechanism (cystinuria, Fanconi syndrome). Examples of each group are given. In cystinuria, besides cystine, lysine, arginine, leucine, and other amino-acids are present in the urine, while the blood shows no increase of cystine or other amino-acids.

In eight cases of Fanconi syndrome the chromatograms show a strong amino-aciduria, which varies from day to day, and in those cases investigated was accompanied by a corresponding change in the blood chromatogram. In one child cystine crystals were found in the bone-marrow, while in three others there was a distinctly stronger cystine spot in the bone-marrow chromatogram than in the peripheral blood. The four children investigated by slit-lamp showed crystalline deposits in the eyes, which provoked photophobia. The diagnostic and pathogenetic importance of these findings is discussed.

DR. S. D. V. WELLER (London). 'Observations on Some Liver Function Tests in Infancy.' Since 1945, 53 infants with prolonged jaundice or hepatomegaly have been investigated. The cases were classified and the findings correlated with clinical impression, progress and histological material.

The Takata-Ara and thymol turbidity tests were nearly always negative before the age of three months even in cases of severe liver damage; over this age they were little more helpful. Alone or together they were less reliable than the clinical impression. The alkaline serum phosphatase was usually raised in these cases but it was useless in differential diagnosis. The value of the Van den Bergh reaction was more limited in infants than adults, particularly by neonatal haemolysis and hepatic immaturity. The remarkably low serum bilirubin level even after months of total obstruction was noted, and the serial biochemistry of a case of biliary atresia illustrated the unpredictable behaviour of these four tests, which varied independently in spite of progressive liver damage.

The conclusion was reached that none of the four tests were of any material help to the clinician, who is obliged either to watch the case while the diagnosis declares itself or to resort to biopsy.

DR. I. A. B. CATHIE. 'Erythrogenesis Imperfecta.' To be published in full.

DR. F. J. W. MILLER (Newcastle-upon-Tyne). 'Visible Primary Tuberculosis.' Primary tuberculosis of skin and mucous membranes has always been regarded as uncommon. Yet in three years 22 cases have been observed: four in eye, three in mouth, 15 on skin. In all except two occurring in large wounds a small primary focus was accompanied by rapid enlargement and later caseation of the regional lymph nodes. All except four were proven tuberculous by bacteriological and histological examination. In eight cases there was preceding injury and in nine a definite contact with an infective adult.

In the skin the characteristic lesion is a small papule which later undergoes ulceration. This primary focus is painless, indolent and, untreated, takes approximately 18 months or two years to heal. The lymph nodes draining the area undergo painless enlargement within two or three weeks of infection and in eight cases caseation followed within eight weeks.

The glandular enlargement is frequently the first recognizable sign and the cause of the patient seeking medical advice. Two cases have shown clinical evidence of haematogenous spread, one child developing a lesion in the right knee and the other generalized miliary tuberculosis followed by fatal meningitis.

Streptomycin therapy brings rapid healing of the primary lesion but its effect upon the regional gland varies with the stage at which therapy is used.

DR. JOHN LORBER (Sheffield). 'The Contact History of 150 Cases of Miliary and Meningeal Tuberculosis.' Drawing on a wide area the Children's Hospital, Sheffield, admitted 150 children suffering from miliary and meningeal tuberculosis in the three years since 1947. An investigation into their history of contact with tuberculosis was begun in 1948 and the prophylactic aspects of the problem were reported with illustrative case histories. The existence of an adult contact was postulated in almost all cases because most children were infected with the human strain of bacillus.

On admission a positive history of contact was obtained in 55 cases, but only five of the children were known previously to be tuberculous, and four of these were under observation at this hospital. Serious faults in the management of the 55 families had caused infection of the children by relatives or friends waiting for admission to a sanatorium or discharged from it as they were thought to be either cured or incurable. No segregation or proper hygienic education was attempted. Adults in sanatoria were allowed home to visit, and children were permitted to visit tuberculous adults in sanatoria.

In 95 cases there was no known contact. Some authorities did not practice examination of contacts because 'meningitis is not infectious.' Of 35 cases who died before this investigation started, the contacts of only nine had been examined. Subsequently contacts in 59 of 60 were examined radiologically.

Of 68 families investigated the source was discovered in 35. Most of these infections could have been prevented by more skill in detecting tuberculosis in adults.

Many cases with primary complexes in the alimentary tract were proved to be of human origin, and milk could be incriminated in only nine as the source of the infection.

Altogether, the source was discovered in 80% of 123 adequately investigated cases.

DR. G. KOMROWER (Manchester). 'Pontine Cisternostomy in Tuberculous Meningitis.' This procedure was devised (1) to direct streptomycin where the largest numbers of tubercles and fibrinous exudate are frequently found; (2) to reduce the number of spinal injections, particularly when general condition and morale were deteriorating because of fear of injection.

After vertical exposure the cerebellar hemisphere is retracted inwards. A nylon tube is passed between nerves V and VII into the pontine cistern and brought to the surface through a separate skin incision. The original incision must be avoided for fear of C.S.F. leak.

Nine cases were treated with five deaths. Three died within five days of operation, all late cases with gross external hydrocephalus and other complications in two cases. One patient showed improvement in morale and cerebrospinal fluid, but died later.

Of living cases (four) two have had no streptomycin treatment for 12 months, one for four months, and one is just finishing. All are markedly improved. Indications for the procedure are: great fear of injections; suggestion of block as indicated by a falling diffusion index, and/or a steady rise in C.S.F. protein; clinical evidence of early hydrocephalus.

It is suggested that if the criteria mentioned above are satisfied, the method might be used early in the treatment of tuberculous meningitis.

PROFESSOR WILFRID GAISFORD (Manchester). 'Delayed Feeding in Premature Neonates.' One of the hazards of prematurity is inhalation of fluids, due to the underdeveloped swallowing and coughing

reflexes, with resultant death from asphyxia. Withholding all fluids till the shock of birth is passed, the lungs more expanded and the reflexes generally better developed, has resulted in minimizing this hazard. During the past two and a half years 231 premature infants weighing between 2 and 5 lb. have been observed with regard to initial weight loss, weight gain by the third week, and the incidence of asphyctic attacks following this régime.

It was found that many infants, even in the smallest weight-groups, would go 100 or more hours before feeding was necessary. The average was 60 hours. Weight loss was the same for all weight-groups and averaged 6 oz., which represented a 14% loss in the lowest weight (2-2½ lb.) and 7% in the 4½-5 lb. group. Weight gain was satisfactory with an average gain over the birth weight of 6½ oz. in all groups.

There was no evidence of any ill-effects of this régime; on the contrary, there were many benefits. Asphyxia due to fluid inhalation was abolished, oedema disappeared more quickly, and the infants were livelier when they did begin to feed.

THE BRITISH PAEDIATRIC ASSOCIATION AND THE SOCIETY OF MEDICAL OFFICERS OF HEALTH

A joint meeting of the British Paediatric Association and the Maternity and Child Welfare, School Health Service, and Fever Hospital groups of the Society of Medical Officers of Health was held in London on November 25-26, 1949. The meeting opened with a symposium on 'The Organization of the Child Health Services.' Sir Wilson Jameson, G.B.E., K.C.B., M.D., F.R.C.P., D.P.H., was in the chair.

The Chairman prefaced the symposium by sketching the social background of paediatrics in Britain today. The findings of the Goodenough Committee had been accepted, and increased grants to medical schools should in the future enable the medical student to emerge better qualified to deal with the day-to-day care of children. Simultaneously the provisions of the National Health Service Act had brought to all mothers and children the care and guidance of a family doctor. The task now was to coordinate for their benefit the services of the family doctor, the paediatrician, and the officers of the local public health department. The part each should play was the subject of the symposium.

Dr. Helen M. M. Mackay (London) read the opening paper on 'The Organization of Child Health Services.' This paper, based on a Chadwick lecture, is published in *Public Health* (63, 37) by permission of the Chadwick Trustees. Dr. Jean Mackintosh (Birmingham) followed with a paper discussing the problem from the point of view of a maternity and child welfare officer (*Public Health*, 63, 41), and Dr. F. Hall (Preston) summarized the comprehensive legislation now forming the basis of a child health service and the administrative steps which should be taken to implement it. Dr. Hall's paper is published in *Public Health* (63, 43).

Professor J. C. Spence (Department of Child Health, University of Durham) chose three points on which to comment: (1) The necessity of obtaining local information and ascertaining local needs; (2) the prevention by a child health service of trauma, tuberculosis, and the acute non-specific infectious diseases, e.g. gastro-enteritis; and (3) the proper use of the health visitor.

A summary of Professor Spence's address, and of the general discussion which followed, is published in *Public Health* (63, 61).

Sir Leonard Parsons, F.R.S., was the Chairman at the afternoon session when Professor A. St. G.Mc.L. Huggett delivered the George Frederick Still Memorial lecture (see p. 101).

The last sessions were devoted to scientific communications and demonstrations. The paper by Dr. J. K. Martin (London) may be found on p. 1 (25, 1) of this journal, and summaries of the following are published in *Public Health*, 63, 61-62.

Drs. K. U. Cross (London) on 'The Measurement of Respiration in the Newborn'; Katherine M. Hirst (London) on 'The Rising Infant Death Rate from Accidental Mechanical Suffocation'; F. J. U. Miller (Newcastle-upon-Tyne) on 'Acute Infections in Infancy'; and H. Stanley Banks (London) on 'Hyperimmune Human Serum Treatment of Whooping Cough.'

REVIEWS

Haemolytic Disease of the Newborn. By M. M. PICKLES. 1949. Blackwell Scientific Publications, Ltd. Pp. 181. (Price 15*s*.)

This monograph is based on a series of more than 100 affected babies observed during a five-year study of haemolytic disease of the newborn. To this firsthand experience of the condition Dr. Pickles brings a wide knowledge of the literature, whose mushroom growth in the last decade is evidenced by a bibliography of more than 350 references.

A historical survey of haemolytic disease is followed by a discussion of the Rhesus and other antigens and antibodies. The mechanism of immunization is considered, and the presentation of the clinical, serological and morbid anatomical features of blood group incompatibility is succeeded by a section on the many aspects of treatment. Prognosis and sequelae are dealt with, and there is an appendix on laboratory procedures.

This is a wholly admirable book, in which every attempt is made to write clearly on a subject of needless obscurity. To the many questions still under discussion Dr. Pickles brings an impartial mind, and she has refreshingly avoided any appearance of prejudice in her conclusions. The style is lucid and the book easy to read, and many doctors whose work deals with the neonatal period will be thankful for plain statements of facts which have often been lost in technical verbiage.

Microphthalmos and Anophthalmos with or without Coincident Oligophrenia. A Clinical and Genetic-statistical study. By TORSTEN SJÖGREN and TAGE LARSSON. 1949. Copenhagen : Ejnar Munksgaard.

Professor Sjögren of the Karolinska Institute of Stockholm is well known for his painstaking and careful studies of the social implications of proven hereditary diseases. The present work is a clinical and genetic analysis of what can be considered the most complete case material on record in any one country. The authors were helped in their efforts by the up-to-date system of notification which exists in Sweden. All forms of blindness are notifiable there and, under the Act of 1896, education of blind children in special schools became compulsory. From 1930 onwards the type of disability had to be included in the census forms, which was an additional help from the standpoint of statistical assessment.

The occurrence of microphthalmos with coincident oligophrenia was first described in Great Britain by Ash in 1922, but not until 1937, when Fraser Roberts' interesting paper on 14 male cases appeared was a detailed genetic-statistical analysis undertaken. Professor Sjögren's monograph deals with a total of 137 proven cases of both types, and the histories cover the period between 1879 and 1946. He found that each of the two disabilities was responsible for 4% of the blind children in Sweden who reach school age. In the later chapters of this very methodical work the questions of sex distribution, mortality, other complicating disabilities, familial and geographical incidence are dealt with. Due prominence is given to aetiology and, in view of much recent controversy in this field, the problem of German measles during pregnancy is discussed. Generally speaking it is, in the author's view, not possible at present to determine the part which exogenous factors play in these disabilities.

This monograph is of outstanding interest to the paediatrician and psychiatrist who seek to combine the clinical, social, and genetic viewpoints. It can be recommended to all those who wish to undertake research on similar lines, because it clearly demonstrates the complexity of some of the problems which must be faced, if such research is going to be of practical value in the field of preventive medicine. The study contains a critical survey of the relevant literature as well as a full bibliography, and is written in clear English.

Epidemiology in Country Practice By W. N. Pickles, M.D., Medical Officer of Health, Aysgarth Rural District, Bristol. 1949. John Wright & Sons, Ltd. Pp. 120. (Price 10*s*. 6*d*.)

This little classic was published in 1939. In 1941 the stock and type were destroyed by enemy action. It is now re-issued and will delight and stimulate paediatricians as well as general practitioners. The publishers state that the new edition is in exactly the same form as the first. There is actually a change in the plates. The first and third are from the same photographs as the original edition, but the reproduction of the first is less good and of the third more true in the current volume. The second plate is new and is yet more beautiful than the attractive but irrelevant view originally published.

The Common Infectious Diseases. By H. STANLEY BANKS, M.A., M.D., F.R.C.S., D.P.H., Physician-Superintendent, Park Hospital, Hither Green, London; Lecturer in Infectious Diseases, the Medical College, St. Bartholomew's Hospital, University of London. 1949. Edward Arnold & Co., London. Pp. 354. (Price 21*s*.)

The author's name on the title page of this volume is a warrant of its integrity and authority. In addition the book is concise and up to date, and may be read for pleasure. We have no hesitation in recommending Dr. Banks's work to children's physicians, for their own and their students' use.

Einfuhrung in die Kinderheilkunde. (Third Ed.) By E. GLANZMANN. 1949. Springer-Verlag. Vienna. Pp. XIII and 986. Illustrations, 287. (Price £3 12*s*.)

Professor Glanzmann's collection of lectures on paediatrics is well known to many and in its third edition has been extensively revised. It is interesting to see how the nearly 200 lectures have been allocated. The British reader will at once note that the newborn period has not received special attention, so that he will have to hunt under various headings for disorders of that age and there is no account of the management of the premature baby. Among new topics are fibrocystic disease of the pancreas, streptomycin, B.C.G., and the rhesus factor. The standard of photographs and printing is high and this can be accepted as an excellent product of the Swiss school of paediatrics.

A Practice of Orthopaedic Surgery. By T. P. MCMURRAY. (Third Ed.) 1949. London: Arnold Edward & Co. Pp. 444. (Price 30*s*.)

The third edition of Professor McMurray's well known book on orthopaedic surgery has been revised and altered in several chapters, but its size and design remain unchanged. Here is to be found a good, straightforward account of orthopaedics based on the work of Hugh Owen Thomas and Robert Jones and reflecting the Liverpool school of thought in which the author has spent his professional life and gained his great experience.

If the views expressed are at times didactic then that makes for compression, and certainly the author has succeeded in presenting his own precepts and practice in a way that is both readable and instructive. He writes, for instance, of congenital dislocation of the hip with easy confidence and has no qualms about the results following his routine manual reductions and plaster of Paris: not for him the modernistic frills of arthrograms or the time-consuming methods of gradual reduction. Nor must the paediatrician look here for academic discussion of some of his borderline orthopaedic problems such as bone changes in lipoidosis and leukaemia, or a consideration of the spastic and athetoid types of cerebral palsy, but he can look (and will not look in vain) for a broad, sound survey of the whole field of orthopaedics tinged with the author's particular shade of individualism.

The Medical Annual (Sixty-seventh Year). 1949. John Wright & Sons. Bristol. Simpkin Marshall 1941. London. Pp. 448. (Price: annual subscription 3 *guineas*.)

The current issue of this classic annual is in general as pleasing as usual. The timely articles on new preparations, such as those on aureomycin by Andrew Wilson and the treatment of malaria by G. M. Findlay are particularly welcome. N. R. Barrett's review of coarctation of the aorta is noteworthy. The illustrations are excellent: among the most interesting are reproductions of Barclay's microradiographs. Synoptic books of this sort should be reliable; unfortunately there seems to have been some carelessness in the production of this one. A doctor who had read the note on pink disease might be excused for giving B.A.L. 3 mg./kilo. four-hourly for nine days, instead of four-hourly for two days, six-hourly for one day, and twelve-hourly for seven days. Minor errors are frequent, for example, Proceedings of the Royal Society for Proceedings of the Royal Society of Medicine (Plate XV); 1914 for 1941 (p. 112); Budding for Buddingh (p. 135); Yllp for Ylppö, and Morrison for Mollison (p. 165).

Juvenile Rheumatism. By G. E. M. SCOTT, M.B., L.R.C.P., late Associate Physician, Children's Hospital, Melbourne. 1948. Melbourne: W. Ramsay (Surg.) Pty. Ltd. Pp. 163. (Price, 25*s*.)

Dr. Scott's monograph is described as a 'clinical survey' and incorporates a study of 645 cases of rheumatic infection attending the Children's Hospital, Melbourne, from 1936 to 1942. The literature, including that relating to epidemiology and control, is reviewed, and the present views regarding etiology are summarized. Whilst it cannot be said that the author has made any outstanding contribution to our understanding of the most baffling disease, his case-material is sufficiently large to be worth analysing, and his painstaking review of the literature will be found useful.

Special Breathing Exercises for Children. Department of Child Health and Medical Illustration, Guy's Hospital. London. 1949. (Price 9*d*.)

This card, simply phrased and attractively illustrated, is designed to teach asthmatic children breathing exercises.

Books Received

Pocken und Pockenschutzimpfung. By M. KAISER, Vorstand des Hygienischen Universitäts-Institutes und Leiter der Bundesstaatlichen Impfstoffgewinnungsanstalt in Wien. 1949. Vienna. Springer-Verlag. Pp. 207. (Price $3.80.)

Taschenbuch der Praktischen Medizin. Edited by J. KOTTMAIER. 1949. Stuttgart: Georg Thieme Verlag. Pp. 788. (Price D.M. 24.)

Die Therapie der übertragbaren Kinderlähmung. By K. HOFMEIER. 1949. Stuttgart: Georg Thieme Verlag. Pp. 112. (Price D.M. 7.50.)

Aktuelle Probleme der Pathologie und Therapie. Edited by H. HOLTHUSEN. 1949. Stuttgart: Georg Thieme Verlag. Pp. 248. (Price D.M. 29.)

Von Der Angst der Kranken. By KARL SCHEELE. 1949. Stuttgart: Georg Thieme Verlag. Pp. 75. (Price D.M. 4.80.)

Die Bazillenruhr. By Ludwig Roemheld. 1949. Stuttgart: Georg Thieme Verlag. Pp. 124. (Price D.M. 10.80.)

L' Alimentation et la Vie

The secretary of the *Société Scientifique D'Hygiene Alimentaire* informs us that their Bulletin, which has been published since 1904, has been altered in form and, since the beginning of 1949, has appeared under the title *L'Alimentation et la Vie*. It appears quarterly, and the annual subscription is 650 francs.